12 BGEM Test Card Specifications

12.1 General BGEM Test Card Specifications

12.1.1 Indications for Use – epoc® System

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.

The **Blood Gas Electrolyte and Metabolite (BGEM) Test Card** panel configuration includes sensors for pH, pCO_2, pO_2, Sodium, Potassium, Ionized Calcium, Chloride, Glucose, Lactate, Creatinine, and Hematocrit.

pH, pCO_2, pO_2 (blood gases) measurements from the epoc Blood Analysis System are used in the diagnosis and treatment of life-threatening acid-base disturbances.

Sodium and **Potassium** measurements from the epoc Blood Analysis System are used in diagnosis and treatment diseases involving electrolyte imbalance.

Ionized Calcium measurements from the epoc Blood Analysis System are used in diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany.

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

Glucose measurements from the epoc Blood Analysis System are used in the diagnosis and treatment of carbohydrate metabolism disorders, including diabetes mellitus and idiopathic hypoglycemia, and of pancreatic islet cell tumors.

Lactate measurements from the epoc Blood Analysis System are used to evaluate the acid-base status and are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity of the blood).

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

Hematocrit measurements from the epoc Blood Analysis System are used to distinguish normal from abnormal states of blood volume, such as anemia and erythrocytosis.

12.2 Test Card Configuration and Use

The epoc Blood Gas Electrolyte and Metabolytes (BGEM) Test Cards include the following measured and calculated Test Results.

epoc BGEM
CT-1006-00-00
pH
pCO_2
pO_2
Sodium Na+
Potassium K+
Ionized Calcium Ca++
Chloride Cl**-**
Glucose Glu
Lactate Lac
Creatinine Crea
Hematocrit Hct
*Bicarbonate cHCO_3**-**
*Calculated Total Carbon Dioxide cTCO_2
*Base excess BE
*Oxygen Saturation cSO_2
*Alveolar Oxygen A
*Arterial Alveolar Oxygen Tension Gradient A-a
*Arterial Alveolar Oxygen Tension Ratio a/A
*Anion Gap AGap
*Anion Gap K+ AGapK
*Estimated Glomerular Filtration Rate:
- GFRmdr (IDMS-traceable MDRD)
- GFRmdr-a (IDMS-traceable MDRD, if African-American)
- GFRckd (CKD-EPI equation)
- GFRckd-a (CKD-EPI equation, if African-American)
- GFRswz (Bedside Schwartz equation)

*Hemoglobin cHgb

** Calculated values*

Note: Some tests are not available in all markets.

12.2.1 Storage Stability

Test Cards must be stored in their Card Pouch at Room Temperature, 15 to 30°C (59 to 86°F), at all times. Never fridge store or allow Test Cards to freeze.

12.2.2 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.2.3 Test Timing

The initiation of a test starts with establishing a communications link between the Host and Reader. Test Card is removed from Card Pouch. Card should be inserted immediately into Reader. During 150-175 second (approximate) calibration period User acquires blood sample for test. After calibration is complete Reader Indicator and epoc Host inform User that Card is ready to receive blood sample. Card is now ready for sample introduction, and sample can be introduced at any time thereafter for up to 450 seconds (7.5 minutes), after which the sample introduction period times-out, and can no longer accept sample. Thirty nine (39) seconds after sample introduction, testing is complete (47 seconds for QA test). Results are then calculated, saved and displayed. Test card can be removed from the Reader and discarded in biohazard waste.

12.2.4 Sample Type

Fresh whole blood from arterial, venous, or capillary sources, is introduced to the card using a Syringe or epoc Care-Fill™ Blood Collection Tube. See "Sample Collection Details" below for the time periods when the blood is considered fresh and thus suitable for testing.

12.2.5 Sample Volume

At least 92 microliters.

Note: The epoc Care-Fill Capillary Tube capacity is 90 microliters plus the volume of air pushed behind the sample when the plunger is fully depressed, which brings it to over 92 microliters.

12.2.6 Sample Collection

The epoc System is designed for point-of-care blood analysis. Test samples immediately after drawing a sample to obtain results that represent patient status with greatest accuracy.

Please note that all epoc System tests are categorized as having moderate complexity (non-waived status) under CLIA.

Always use ISO 80369-7 compliant Syringe for sample introduction.

The epoc System is intended to be used with fresh whole blood samples only. Do not use clotted samples.

Always wear protective gloves when handling blood samples.

The specimen used to fill a Test Card must be collected and handled properly to ensure that the results represent Patient's current status.

Blood samples must be collected according to the facility's policies and procedures. Always follow the specific instructions provided by other medical manufacturers when considering information in this section.

When anticoagulants are needed, use exclusively heparin for the anticoagulant.

See table below for additional options for specific tests and sample collection methods.

Test	Sample Collection Details *(see also References at the end of the present subsection)*		
	Syringes • **1 or 3 mL plastic** • **Without anticoagulant must be run within 3-5 min** • **With Li or Na heparin** • **With balanced heparin**	**Evacuated Tubes** • **With Li or Na heparin** • **Without anticoagulant must be run immediately Note that clot activators may be present in some collection devices**	**Capillary Tubes** • **epoc Care-Fill Capillary Tubes only**
***p*O₂**	• Non-iced syringes [1,2] • Test in less than 30 min[1,2]	• Not recommended[1]	• Test in less than 5 min recommended
pH/*p*CO₂*	• Test in less than 30 min[1,2]	• Test in less than 30 min[1,2]	• Test in less than 5 min recommended
Ionized Calcium	• With Li or Na heparin only if <10 IU/mL[3] • With balanced heparin only if <70 IU/mL[3] • Test in less than 30 min to avoid artifacts of metabolic activity[1,2,3]	• With Li or Na heparin only if <10 IU/mL[3] • Test in less than 30 min to avoid artifacts of metabolic activity[1,2,3]	• Care-Fill capillary tubes contain 65 IU/mL of calcium balanced lithium heparin • Test in less than 5 min recommended
Glucose	• Test in less than 30 min to avoid effects of glycolysis[11,12]	• With Li or Na heparin only (do not use NaF) • Test in less than 30 min to avoid effects of glycolysis[11,12]	• Test in less than 5 min recommended
Lactate	• Test in less than 5 min to avoid effects of glycolysis[13]	• With Li or Na heparin only (do not use NaF) • Test in less than 5 min to avoid effects of glycolysis[13]	• Test in less than 5 min recommended
Hematocrit	• Immediate testing is recommended in order to avoid RBC settling. (*Note: Re-suspension of RBC requires an air bubble of significant volume[4]*)	• With Li or Na heparin only (do not use EDTA) • Test in less than 1 h to avoid effects of glycolysis and electrolyte shifts[14]	• Immediate testing is recommended in order to avoid RBC settling
All other tests	• Test in less than 1 h to avoid effects of glycolysis and electrolyte shifts[14]	• With Li or Na heparin[**] • Test in less than 1 h to avoid effects of glycolysis and electrolyte shifts[14]	• Test in less than 5 min recommended

*Non-iced samples recommended. Iced samples may cause increased pH internal quality control failures.

[**] Use of evacuated collection tubes containing Na heparin may cause a positive error on the sodium results.[15] See also Section 12.6.7 D.

12.2.7 Interpretation of Results

If Patient Test Results are inconsistent with clinical assessment, a fresh Patient sample should be collected and tested on another card.

Look further in this section for information on factors affecting results of various sensors. Certain substances, such as drugs, may affect the Test Results[5-7].

12.2.8 Measurement ranges (some values may be rounded)

Note: The tables below provide the data for reference ranges as published in literature (see references for details). Institutions should confirm their own reference range values.

Measured Parameters			
Test	**Units of Measure**	**Measurement Range**	**Reference Range[8-10]**
pH	pH units	6.5 – 8.0	7.35 – 7.45 arterial
			7.32 – 7.43 venous
***p*CO₂**	mm Hg	5 – 250	35 – 48 arterial
			41 – 51 venous
	kPa	0.7 – 33.3	4.7 – 6.4 arterial
			5.4 – 6.8 venous
***p*O₂**	mm Hg	5 – 750	83 – 108 arterial**
	kPa	0.7 - 100	11.1 – 14.4 arterial**
Na+	mmol/L	85 – 180	138 – 146
	mEq/L		
K+	mmol/L	1.5 – 12.0	3.5 – 4.5
	mEq/L		
Ca++	mmol/L	0.25 – 4.00	1.15 – 1.33
	mg/dL	1.0 – 16.0	4.6 – 5.3
	mEq/L	0.5 – 8.0	2.3 – 2.7
Cl-	mmol/L	65 – 140	98 – 107
	mEq/L		
Glu	mmol/L	1.1 – 38.5	4.1 – 5.5
	mg/dL	20 – 700	74 – 100
	g/L	0.20 – 7.00	0.74 – 1.00
Lac	mmol/L	0.30 – 20.00	0.36 – 0.75 arterial
			0.56 – 1.39 venous
	mg/dL	2.7 – 180.2	3.2 – 6.8 arterial
			5.0 – 12.5 venous
	g/L	0.03 – 1.80	0.03 – 0.07 arterial
			0.05 – 0.12 venous
Crea	mg/dL	0.30 – 15.00	0.51 – 1.19
	μmol/L	27 – 1326	45 – 105
Hct	% PCV	10 – 75	38 – 51
	L/L	0.10 – 0.75	0.38 – 0.51

* Some units for Glucose may not be available in all regions.

** As per CLSI C46-A2[1], arterial blood samples are preferred for blood gas analysis. Therefore, reference ranges for arterial blood gases may not be directly applied to venous and capillary blood gases. Note that there are conflicting reports[16-21] regarding the validity of pO_2 analysis performed on arterialized capillary blood samples, compared to arterial pO_2. Variability in both capillary collection process and in capillary blood itself may affect test results for pH, pO_2, pCO_2, and calculated sO_2 of capillary samples.

Calculated Parameters			
Test	**Units of Measure**	**Measurement Range**	**Reference Range[8-10,22]**
$cHCO_3$-	mmol/L	1 – 85	21 – 28 arterial
			22 – 29 venous
	mEq/L	1 – 85	21 – 28 arterial
			22 – 29 venous
$cTCO_2$	mmol/L	5 – 50	22 – 29 arterial
			23 – 30 venous
	mEq/L	5 – 50	22 – 29 arterial
			23 – 30 venous
BE(ecf)	mmol/L	-30 – +30	-2 – +3
	mEq/L		
BE(b)	mmol/L	-30 – +30	-2 – +3
	mEq/L		
cSO_2	%	0 – 100	94 – 98 arterial
A	mmHg	5-800	†
	kPa	0.67-106.64	†
A–a	mmHg	1-800	†
	kPa	0.13-106.64	†
a/A	%	0-100	†
	fraction	0-1	†
AGap	mmol/L	-14 – +95	7 – 16
	mEq/L		
AGapK	mmol/L	-10 – +99	10 – 20
	mEq/L		
GFRmdr, GFRmdr-a	mL/min/1.73m^2	2 – 60 or >60*	†
GFRckd, GFRckd-a	mL/min/1.73m^2	1 – 225	†
GFRswz	mL/min/1.73m^2	1 – 275	†
cHgb	g/dL	3.3 – 25	12 – 17
	mmol/L	2.0 – 15.5	7.4 – 10.6
	g/L	33 – 250	120 – 170

* *Numeric values will be reported for values between 2-60 mL/min/1.73 m^2. Values >60 will be reported as > 60 mL/min/1.73 m^2. This range is based on the specific National Kidney Disease Education Program (NKDEP) recommendation for reporting GFRmdr values. These ranges are based on the specific National Kidney Disease Education Program (NKDEP) recommendation for reporting GFRmdr values. Please refer to the following web link: http://nkdep.nih.gov/lab-evaluation/gfr/reporting.shtml. GFRmdr > 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.*

† *Widely accepted reference ranges are not well established. Institutions should establish and set their own reference range values.*

12.2.9 References

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12.3 pH

pH is measured by potentiometry using a pH selective membrane electrode. The concentration of hydrogen ions is obtained from the measured potential using the Nernst equation.

12.3.1 Indications for Use

The pH 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.

Measurement of pH, pCO_2, pO_2 (blood gases) is used in the diagnosis and treatment of life-threatening acid-base disturbances.

12.3.2 Contents

Each Test Card incorporating a pH test contains a hydrogen ion sensing electrode with a hydrogen ion selective membrane, a reference electrode and a calibrator fluid containing a known concentration of pH buffer salts.

12.3.3 Traceability

Values of pH assigned to controls and calibrator fluids are traceable to NIST standards.

12.3.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.3.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.3.6 Measurement Range

	Measurement Range	**Reference Range[1]**	
		Arterial	**Venous**
pH	6.5 – 8.0	7.35 – 7.45	7.32 – 7.43

12.3.7 Temperature Correction

pH is a temperature dependent quantity, measured at 37°C on the epoc System. The pH value can be corrected to the Patient's temperature. Patient temperature is entered on the Test Information Page of the Reader Tab on the epoc Host (see Section 3 "epoc System Operation" in this manual).

The pH at the Patient's temperature (T, °C) is calculated as follows[2]:

$$pH(T) = pH - 0.0147(T - 37) + 0.0065(7.4 - pH)(T - 37)$$

12.3.8 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[3] for method comparison studies, CLSI EP07-A2[4] for interference studies and CLSI EP05-A2[10] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	pH units	7.641	0.008	0.1
Low Level	pH units	7.045	0.010	0.1

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with pH values spanning the reportable range. Linearity is reported versus an in-house standard pH electrode method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
pH	6.4 – 7.9	pH units	1.021	-0.15	0.999

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[3]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[6] in the lab (two test occasions), and then at three point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

pH	Lab 1	Lab 2	POC 1	POC 2	POC 3	All	All*
N	34	24	35	27	22	142	149
Sxx	0.016	0.012	0.010	0.010	0.015	0.013	0.014
Syy	0.005	0.006	0.006	0.006	0.008	0.006	0.007
Intercept	0.152	0.006	0.448	-0.772	-0.367	0.029	0.251
Slope	0.978	0.999	0.938	1.104	1.050	0.995	0.966
Syx	0.019	0.021	0.013	0.015	0.024	0.018	0.020
Xmin	6.991	7.085	7.243	7.223	7.174	6.991	6.770
Xmax	7.592	7.557	7.507	7.522	7.557	7.592	7.982
R	0.993	0.985	0.961	0.981	0.985	0.987	0.991
Mean Bias (pH units)							-0.007

*This data set includes Patient samples spiked with NaOH for extended data range.

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[7] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

pH	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (pH units)
Lab	77	0.011	0.010	0.366	0.952	0.017	7.175	7.542	0.975	0.011

D. Limitations and Interferences

Exposure of the sample to air will affect pH, pCO_2, pO_2 and ionized calcium results due to the sample equilibration with the gas levels in the air, with pH affected by the pCO_2 change[9] and ionized calcium affected by the pH change[8]. Air contains less than 1 mmHg pCO_2 and about 150-180 mmHg pO_2. Do not introduce air bubbles into a collection device. If present, air bubbles should be removed immediately after collection.

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[4] was performed in-house on the epoc pH sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The pH bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Samples contaminated with benzalkonium salts used as coatings for in-dwelling lines may cause lower pH results[2]. For proper line-flushing procedures refer to CLSI H11-A4[5].

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 1 mmol/L iodide, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 35 mmol/L bromide, 2.64 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 20 mmol/L NaCl, 8 mmol/L KCl, 3 mmol/L $CaCl_2$, 10 to 120 mmHg pCO_2, pH 6.9 to 7.7, +20 mmol/L bicarbonate, 10 mmol/L lactate, +20% PCV Hct, 3% to 11% total protein, 0.8g/dL lipids, 9.1 mmol/L cholesterol, 20 mmol/L β-hydroxybutyrate, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

E. References

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12.4 pCO_2

pCO_2 is measured by potentiometry using a membrane covered pH sensing electrode[9,10]. The electrode voltage is proportional to the dissolved carbon dioxide concentration through the Nernst equation.

12.4.1 Indications for Use

The pCO_2 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.

Measurement of pH, pCO_2, pO_2 (blood gases) is used in the diagnosis and treatment of life-threatening acid-base disturbances.

12.4.2 Contents

Each Test Card incorporating a pCO_2 test contains a pH sensing electrode overlaid with a bicarbonate containing membrane, a carbon dioxide permeable membrane, a reference electrode and a calibrator fluid containing a known concentration of dissolved carbon dioxide.

12.4.3 Traceability

Dissolved carbon dioxide concentration values assigned to controls and calibrator fluids are traceable to NIST standards via commercially available certified gas standards.

12.4.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.4.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.4.6 Measurement Range

	Measurement Range	**Reference Range[2]**	
		Arterial	**Venous**
pCO_2	5 – 250 mmHg	35 – 48 mmHg	41 – 51 mmHg
	0.7 – 33.3 kPa	4.7 – 6.4 kPa	5.4 – 6.8 kPa

12.4.7 Temperature Correction

pCO_2 is a temperature dependent quantity, measured at 37°C on the epoc System. The pCO_2 value can be corrected to the Patient's temperature. Patient temperature is entered on the Test Information Page of the Reader Tab on the epoc Host (see Section 3 "epoc System Operation" in this manual).

The pCO_2 at the Patient's temperature (T, °C) is calculated as follows[1]

$$pCO_2\ (T) = pCO_2 \times 10^{0.019(T - 37)}$$

12.4.8 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[4] for method comparison studies, CLSI EP07-A2[7] for interference studies and CLSI EP05-A2[11] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mmHg	67.9	2.5	3.7
Low Level	mmHg	20.8	0.7	3.4

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with pCO_2 values spanning the reportable range. Linearity is reported versus an in-house standard blood gas method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
$\boldsymbol{pCO_2}$	10-230	mmHg	1.058	-3.6	0.999

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[4]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[5] in the lab (two test occasions), and then at three (3) point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

pCO_2	Lab 1	Lab 2	POC 1	POC 2	POC 3	All
N	34	24	35	28	22	143
Sxx	1.4	2.1	0.6	1.5	1.7	1.5
Syy	1.3	1.3	0.6	1.1	1.2	1.1
Intercept	-2.0	-1.2	-6.1	5.0	1.0	-0.9
Slope	1.048	1.055	1.167	0.911	0.983	1.041
Syx	3.1	2.3	1.6	2.3	2.4	2.4
Xmin	19.7	26.7	35.6	29.1	23.6	19.7
Xmax	112.2	92.5	54.4	55.6	63.0	112.2
R	0.993	0.991	0.967	0.949	0.978	0.990
Mean Bias (mmHg)						0.8

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[6] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

pCO_2	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (mmHg)
Lab	77	1.5	0.8	1.6	0.924	1.97	27.6	101.5	0.987	-1.445

D. Limitations and Interferences

Exposure of the sample to air will affect pH, pCO_2, pO_2 and ionized calcium results due to the sample equilibration with the gas levels in the air, with pH affected by the pCO_2 change[3] and ionized calcium affected by the pH change[8]. Air contains less than 1 mmHg pCO_2 and about 150-180 mmHg pO_2. Do not introduce air bubbles into a collection device. If present, air bubbles should be removed immediately after collection.

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[7] was performed in-house on the epoc pCO_2 sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The pCO_2 bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Bromide will increase the pCO_2 by 0.19 mmHg/mM bromide

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 0.4 mmol/L iodide, 2.64 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 0.7 mM metronidazole, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 20 mmol/L NaCl, 8 mmol/L KCl, 3 mmol/L $CaCl_2$, pH 6.9 to 7.7, +20 mmol/L bicarbonate, 10 mmol/L lactate, +20% PCV Hct, 3% to 11% total protein, 0.8g/dL lipids, 9.1 mmol/L cholesterol, 20 mmol/L β-hydroxybutyrate, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

E. References

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4. CLSI. Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline, second edition, CLSI document EP09-A2 (ISBN 1-56238-472-4), CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2002.
5. i-STAT 300, Abbott Point of Care Inc., 104 Windsor Center Drive, East Windsor, NJ 08520, "i-STAT" is a registered trademark of Abbott Laboratories.
6. Radiometer ABL 735, Radiometer Medical ApS, Åkandevej 21, DK-2700 Brønshøj, Denmark, "Radiometer" and "ABL" are registered trademarks of Radiometer Medical ApS.
7. CLSI. Interference Testing in Clinical Chemistry; Approved Guideline, CLSI document EP07-A2 (ISBN 1-56238-480-5), CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2002.
8. D.B. Endres and R.K. Rude, Chapter 49 (p. 1901) of Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, fourth edition, C.A. Burtis, E.R. Ashwood, and D.E. Bruns eds., Elsevier Saunders, St. Louis, 2006.
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11. CLSI. Evaluation of Precision in Clinical Chemistry Devices; Approved Guideline, second edition, CLSI document EP05-A2 (ISBN 1-56238-542-9), CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.
12. Reference Ranges Table 41-20 in Tietz Textbook of Clinical Chemistry, second edition, C.A. Burtis and E.R. Ashwood eds., Elsevier Saunders, Philadelphia, 1994.

12.5 pO_2

pO_2 is measured by amperometry using a membrane covered oxygen sensing cathode electrode. The oxygen reduction current is proportional to the dissolved oxygen concentration[9].

12.5.1 Indications for Use

The pO_2 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.

Measurement of pH, pCO_2, pO_2 (blood gases) is used in the diagnosis and treatment of life-threatening acid-base disturbances.

12.5.2 Contents

Each Test Card incorporating a pO_2 test contains a sensing electrode with a oxygen permeable membrane, a reference electrode, a counter electrode and a calibrator fluid containing a known concentration of dissolved oxygen.

12.5.3 Traceability

Dissolved oxygen concentration values assigned to controls and calibrator fluids are traceable to NIST standards via commercially available certified gas standards.

12.5.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.5.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.5.6 Measurement Range

	Measurement Range	**Reference Range[3], Arterial**
pO_2	5 – 750 mmHg	83 – 108 mmHg
	0.7 – 100 kPa	11.1 – 14.4 kPa

Refer to Sections 5.2.2, 5.2.3, and 5.2.4 of CLSI C46-A2[1] for more information on sample types.

12.5.7 Temperature Correction

pO_2 is a temperature dependent quantity, measured at 37°C on the epoc System. The pO_2 value can be corrected to the Patient's temperature. Patient temperature is entered on the Test Information Page of the Reader Tab on the epoc Host (see Section 3 "epoc System Operation" in this manual).

The pO_2 at the Patient's temperature (T, °C) is calculated as follows[1]

$$pO_2\,(T) = pO_2 \times 10^{\frac{5.49x10^{-11}\,pO_2^{3.88}+0.071}{9.71x10^{-9}\,pO_2^{3.88}+2.30}(T-37)}$$

12.5.8 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[4] for method comparison studies, CLSI EP07-A2[7] for interference studies and CLSI EP05-A2[10] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mmHg	181.7	6.2	3.4
Low Level	mmHg	63.8	4.1	6.4

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with pO_2 values spanning the reportable range. Linearity is reported versus an in-house standard blood gas method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
***p*O₂**	10 – 750	mmHg	1.022	-3.9	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[4]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[5] in the lab (two test occasions), and then at three point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

pO_2	Lab 1	Lab 2	POC 1	POC 2	POC 3	All
N	34	23	35	28	22	142
Sxx	2.6	4.3	3.2	6.2	2.7	4.6
Syy	1.7	3.5	3.0	2.9	2.6	2.7
Intercept	-6.5	-3.1	-1.3	0.3	-3.9	-1.7
Slope	1.142	1.006	1.083	1.041	1.090	1.053
Syx	8.5	4.5	4.5	4.9	4.2	6.6
Xmin	26.0	35.0	43.5	36.0	35.5	26.0
Xmax	174.5	226.5	185.0	187.5	166.0	226.5
R	0.977	0.995	0.995	0.990	0.994	0.978
Mean Bias (mmHg)						1.2

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[6] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

pO_2	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (mmHg)
Lab	77	3.4	3.7	-0.8	1.117	5.1	10.2	278.5	0.997	5.0

D. Limitations and Interferences

Exposure of the sample to air will affect pH, pCO_2, pO_2 and ionized calcium results due to the sample equilibration with the gas levels in the air, with pH affected by the pCO_2 change[1] and ionized calcium affected by the pH change[8]. Air contains less than 1 mmHg pCO_2 and about 150-180 mmHg pO_2. Do not introduce air bubbles into a collection device. If present, air bubbles should be removed immediately after collection.

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[7] was performed in-house on the epoc pO_2 sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The pO_2 bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Metronidazole will cause an average bias of +4 mmHg/100µM metronidazole. Note that as per CLSI EP07-A2[7], therapeutic levels of metronidazole range between 35 and 234µM.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 1 mmol/L iodide, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 37.5 mmol/L bromide, 2.7% halothane, 2.64 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 20 mmol/L NaCl, 8 mmol/L KCl, 3 mmol/L $CaCl_2$, 10 to 120 mmHg pCO_2, pH 6.9 to 7.7, +20 mmol/L bicarbonate, 10 mmol/L lactate, +20% PCV Hct, 3% to 11% total protein, 0.8g/dL lipids, 9.1 mmol/L cholesterol, 20 mmol/L β-hydroxybutyrate, 1 mmol/L L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

E. References

1. CLSI. Blood Gas and pH Analysis and Related Measurements; Approved Guideline, CLSI C46-A2, Vol. 29, No. 8, Blood gas and pH analysis and related measurements- Approved Guideline, second edition, Wayne, Pennsylvania, USA, 2009.
2. M.G. Scott, V.A. LeGrys and J.S. Klutts, Chapter 27 of Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, fourth rdition, C.A. Burtis, E.R. Ashwood, and D.E. Bruns eds., Elsevier Saunders, St. Louis, 2006.
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5. i-STAT 300, Abbott Point of Care Inc., 104 Windsor Center Drive, East Windsor, NJ 08520, "i-STAT" is a registered trademark of Abbott Laboratories.
6. Radiometer ABL 735, Radiometer Medical ApS, Åkandevej 21, DK-2700 Brønshøj, Denmark, "Radiometer" and "ABL" are registered trademarks of Radiometer Medical ApS.
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12.6 Sodium (Na+)

Sodium is measured by potentiometry using an ion selective membrane electrode. The concentration of sodium ions is obtained from the measured potential using the Nernst equation. The epoc sodium measurement is an undiluted (direct) method. Values may differ from those obtained by dilutional (indirect) methods.[1]

12.6.1 Indications for Use

The sodium 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.

Measurement of sodium is used in diagnosis and treatment of diseases involving electrolyte imbalance.

12.6.2 Contents

Each Test Card incorporating a sodium test contains a sodium sensing electrode with a sodium selective membrane, a reference electrode and a calibrator fluid containing a known concentration of sodium salts.

12.6.3 Traceability

Values of sodium ion concentration assigned to controls and calibrator fluids are traceable to NIST standards.

12.6.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.6.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.6.6 Measurement Range

	Measurement Range	**Reference Range[2,3]**
Na+	85 – 180 mmol/L	138 – 146 mmol/L
	85 – 180 mEq/L	138 – 146 mEq/L

12.6.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[4] for method comparison studies, CLSI EP07-A2[5] for interference studies and CLSI EP05-A2[12] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mmol/L	164.3	0.98	0.6
Low Level	mmol/L	112.5	0.76	0.7

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with sodium concentration spanning the reportable range. Linearity is reported versus an in-house standard ion selective electrode method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
Na+	80-190	mmol/L	0.973	3.8	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[4]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one (1) hospital study, the epoc System was compared with the i-STAT 300[6] in the lab (2 test occasions) then at three (3) point-of-care sites:

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

Na+	Lab 1	Lab 2	POC 1	POC 2	POC 3	All	All*
N	34	24	35	27	22	142	156
Sxx	0.79	0.61	0.48	0.62	0.45	0.61	0.62
Syy	0.77	0.82	0.84	0.89	0.66	0.80	0.88
Intercept	22.2	8.4	5.3	27.9	28.9	8.8	-9.6
Slope	0.839	0.944	0.963	0.812	0.803	0.941	1.077
Syx	2.18	2.07	1.67	1.38	2.46	2.05	2.22
Xmin	125	123	130	135	130	123	123
Xmax	143	145	143	146	146	146	179
R	0.822	0.914	0.888	0.847	0.813	0.880	0.953
Mean Bias (mM)							0.77

*This data set includes Patient samples spiked with NaCl for extended data range.

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[7] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

Na+	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (mM)
Lab	77	0.78	0.79	19.1	0.881	1.81	131	160	0.924	2.67

D. Limitations and Interferences

Similar to other dry reagent methods, a decrease (increase) of total protein will increase (decrease) Na+ by 1.3 mM/(g/dL) versus a direct method. The epoc Na+ result tracks the reading of an indirect (dilutional) method[1,8,9].

Concordant with direct methods, hyperlipidemia does not affect the Na+ measurement[8.9]. The effect of Intralipid was tested up to 5% (lipid vol)/(plasma vol) and was found to be clinically insignificant.

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[5] was performed in-house on the epoc sodium sensor. In each of these tests a whole blood specimen was aliquoted into two (2) samples. The test sample was spiked by addition of an interferent, while the control sample was spiked by the addition of the solvent of the interferent. The sodium bias between the mean of six (6) replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Use of evacuated collection tubes containing Na heparin may give erroneously high sodium results. The effect from the sodium heparin in these tubes is to increase the sodium result by approximately 1-2 mmol/L[13];
- 20 mmol/L β-hydroxybutyrate will decrease Na+ by 3 mmol/L;
- 16 mmol/L bromide will increase sodium by 5 mmol/L;
- Samples contaminated with benzalkonium salts used as coatings for in-dwelling lines may cause significant elevation of sodium results[10]. For proper line-flushing procedures refer to CLSI H11[11];
- Teriflunomide will have no significant effect up to 720 µmol/L (19.3 mg/dL), after which it will decrease sodium readings by as much as -0.67 mmol/L per 100 µmol/L of teriflunomide. The therapeutic level for teriflunomide is in the range of 1–370 µmol/L.[14]

Systematic errors in sodium readings may occur with over 20% hemodilution of plasma using solutions that are not consistent with the ionic characteristics of plasma, such as Normal Saline, Ringer's (Baxter Healthcare Corporation), and 10% Dextrose (Baxter Healthcare Corporation).

Hemodilution is associated with priming cardiopulmonary bypass pumps, plasma volume expansion, or other fluid administration therapies.

Such errors are prevented when physiologically balanced multi-electrolyte intravenous solutions containing low mobility anions that match the ionic characteristics of plasma, such as Plasma-Lyte™-A (Baxter Healthcare Corporation), Lactated Ringer's (Baxter Healthcare Corporation), Lactated Ringer's + 5% Dextrose injection (Baxter Healthcare Corporation), Plasbumin™-5 (Telacris Biotherapeutics), Pentaspan™ (Bristol-Myers Squibb), and Voluven™ (Fresenius Kabi) are used.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 0.7 mmol/L iodide, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 3 µmol/L dobutamine , 2.5 mmol/L tolbutamide, 2.64 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 0.7 mM metronidazole, 719 µmol/L (19.2 mg/dL) leflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 8 mmol/L KCl, 3 mmol/L $CaCl_2$, 10 to 120 mmHg pCO_2, pH 6.9 to 7.7, +20 mmol/L bicarbonate, +20% PCV Hct, 9.1 mmol/L cholesterol, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

E. References

1. M.G. Scott, V.A. LeGrys and J.S. Klutts, Chapter 27 of Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, fourth edition, C.A. Burtis, E.R. Ashwood, and D.E. Bruns eds., Elsevier Saunders, St. Louis, 2006.
2. Reference Ranges Table 56-1 in Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, fourth edition, C.A. Burtis, E.R. Ashwood, and D.E. Bruns eds., Elsevier Saunders, St. Louis, 2006.
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12.7 Potassium (K+)

Potassium is measured by potentiometry using an ion selective membrane electrode. The concentration of potassium ions is obtained from the measured potential using the Nernst equation. The epoc potassium measurement is an undiluted (direct) method. Values may differ from those obtained by dilutional (indirect) methods.[1]

12.7.1 Indications for Use

The potassium 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.

Measurement of potassium is used in diagnosis and treatment of diseases involving electrolyte imbalance.

12.7.2 Contents

Each Test Card incorporating a potassium test contains a potassium sensing electrode with a potassium selective membrane, a reference electrode, and calibrator fluid containing a known concentration of potassium salts.

12.7.3 Traceability

Values of potassium ion concentration assigned to controls and calibrator fluids are traceable to NIST standards

12.7.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.7.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.7.6 Measurement Range

	Measurement Range	**Reference Range[2]**
K+	1.5 – 12.0 mmol/L	3.5 – 4.5 mmol/L
	1.5 – 12.0 mEq/L	3.5 – 4.5 mEq/L

If a K result is higher than as per clinical status, the blood sample should be spun down and evaluated for hemolysis either visually or on a lab analyzer.

12.7.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[3] for method comparison studies, CLSI EP07-A2[4] for interference studies and CLSI EP05-A2[9] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mmol/L	6.09	0.06	1.0
Low Level	mmol/L	2.1	0.04	1.9

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with potassium concentration spanning the reportable range. Linearity is reported versus an in-house standard ion selective electrode method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
K+	1.5-12	mmol/L	1.006	0.03	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[3]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[5] in the lab (two test occasions), and then at three (3) point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

K+	Lab 1	Lab 2	POC 1	POC 2	POC 3	All	All*
N	34	24	35	27	22	142	146
Sxx	0.040	0.061	0.040	0.061	0.030	0.047	0.048
Syy	0.043	0.052	0.045	0.045	0.045	0.046	0.049
Intercept	-0.164	-0.144	-0.171	-0.134	0.134	-0.044	-0.018
Slope	1.056	1.042	1.051	1.057	0.971	1.021	1.013
Syx	0.088	0.114	0.057	0.077	0.114	0.094	0.094
Xmin	2.5	3.0	2.6	2.9	3.3	2.5	2.5
Xmax	6.1	4.8	5.1	4.9	6.7	6.7	7.8
R	0.991	0.979	0.993	0.993	0.988	0.989	0.993
Mean Bias (mM)							0.04

*This data set includes Patient samples spiked with KCl for extended data range.

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[6] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

K+	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (mM)
Lab	77	0.057	0.044	-0.073	1.026	0.090	2.4	7.1	0.996	0.05

D. Limitations and Interferences

Sample hemolysis will cause elevated potassium values. Improper sample collection technique may cause variation in potassium values due to hemolysis[1].

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[4] was performed in-house on the epoc potassium sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of an interferent, while the control sample was spiked by the addition of the solvent of the interferent. The potassium bias between the mean of six (6) replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Samples contaminated with benzalkonium salts used as coatings for in-dwelling lines may cause significant elevation of potassium results[7]. For proper line-flushing procedures refer to CLSI H11-A4[8].

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 0.7 mmol/L iodide, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 38 mmol/L bromide, 3 µmol/L dobutamine , 2.5 mmol/L tolbutamide, 2.64 mmol/L propofol, 0.7 mmol/L

cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 0.7 mM metronidazole, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 20 mmol/L NaCl, 3 mmol/L $CaCl_2$, 10 to 120 mmHg pCO_2, pH 6.9 to 7.7, +20 mmol/L bicarbonate, 10 mmol/L lactate, +20% PCV Hct, 3% to 11% total protein, 0.8g/dL lipids, 9.1 mmol/L cholesterol, 20 mmol/L β-hydroxybutyrate, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

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12.8 Ionized Calcium (Ca++)

Note: ***Ca++*** *and* ***iCa*** *are equivalent analyte acronyms that stand for ionized calcium.*

Ionized calcium is measured by potentiometry using an ion selective membrane electrode. The concentration of calcium ions is obtained from the measured potential using the Nernst equation.

12.8.1 Indications for Use

The ionized calcium 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.

Measurement of ionized calcium is used in diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany.

12.8.2 Contents

Each Test Card incorporating an ionized calcium test contains a calcium ion sensing electrode with a calcium selective membrane, a reference electrode and a calibrator fluid containing a known concentration of calcium salts.

12.8.3 Traceability

Values of calcium ion concentration assigned to controls and calibrator fluids are traceable to NIST standards

12.8.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.8.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.8.6 Measurement Range

	Measurement Range	**Reference Range[1]**
Ca++	0.25 – 4.00 mmol/L	1.15 – 1.33 mmol/L
	1.0 – 16.0 mg/dL	4.6 – 5.3 mg/dL
	0.5 – 8.0 mEq/L	2.3 – 2.7 mEq/L

12.8.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[2] for method comparison studies, CLSI EP07-A2[3] for interference studies and CLSI EP05-A2[11] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mmol/L	1.56	0.018	1.2
Low Level	mmol/L	0.66	0.011	1.7

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with ionized calcium concentration spanning the reportable range. Linearity is reported versus an in-house standard ion selective electrode method with traceability to NIST standards.

	Test Range	Units	Slope	Intercept	R
Ca++	0.6-3.7	mmol/L	1.017	-0.01	0.999

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[2]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[4] in the lab (two test occasions), and then at three point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

Ca++	Lab 1	Lab 2	POC 1	POC 2	POC 3	All	All*
N	34	24	35	28	22	143	156
Sxx	0.016	0.019	0.014	0.017	0.015	0.016	0.016
Syy	0.011	0.014	0.017	0.014	0.015	0.014	0.015
Intercept	0.003	0.050	0.157	0.106	0.103	0.102	-0.026
Slope	0.980	0.953	0.851	0.925	0.923	0.908	1.021
Syx	0.025	0.033	0.020	0.016	0.024	0.029	0.031
Xmin	0.8	0.9	1.1	1.0	1.0	0.8	0.80
Xmax	1.4	1.6	1.3	1.3	1.3	1.6	2.20
R	0.974	0.961	0.891	0.978	0.939	0.943	0.985
Mean Bias (mM)							0.014

*This data set includes Patient samples spiked with $CaCl_2$ for extended data range.

Clinical Site Method Comparison 2: In another hospital study the epoc System was compared with the Radiometer ABL 735[5] in the lab.

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

Ca++	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (mM)
Lab	77	0.023	0.016	-0.045	1.025	0.040	0.34	1.52	0.981	-0.013

D. Limitations and Interferences

Specimen choice, collection technique, anti-coagulant type and level as well as sample handling will affect the concentration of ionized calcium[6].

Exposure of the sample to air will affect pH, pCO_2, pO_2 and ionized calcium results due to the sample equilibration with the gas levels in the air, with pH affected by the pCO_2 change[7] and ionized calcium affected by the pH change[8]. Air contains less than 1 mmHg pCO_2 and about 150-180 mmHg pO_2. Do not introduce air bubbles into a collection device. If present, air bubbles should be removed immediately after collection.

Whole blood specimens should not be over-diluted with liquid anti-coagulants or other solutions used in therapies as this may alter results. Refer to 12.2.6 Sample Collection.

Interference testing[3] was performed in-house on the ionized calcium sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The ionized calcium bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- 20 mmol/L β-hydroxybutyrate will decrease Ca++ by 0.038 mmol/L;
- 4.3 mmol/L salicylate or acetyl salicylate will decrease Ca++ by 0.06 mmol/L. Therapeutic range for salicylate is 0.1mM to 2 mM (1.4 mg/dL to 27.4 mg/dL)[13];
- 10 mmol/L bromide will increase Ca++ by 0.05 mmol/L;
- 1 mmol/L sodium perchlorate will decrease Ca++ by 0.23 mmol/L. The therapeutic level for perchlorate is in the range of 100–1000 mg/dL. No effect has been observed in persons exposed at 0.5 mg/dL or below[12];
- Leflunomide will have no significant effect up to a concentration of 130 µmol/L (3.6 mg/dL), after which it will decrease Ca++ readings by as much as -0.03 mmol/L per 100 µmol/L of leflunomide. The therapeutic level for leflunomide is in the range of 1–370 µmol/L[14];
- Teriflunomide will have no significant effect up to a concentration of 75 µmol/L (2.0 mg/dL), after which it will decrease Ca++ readings by as much as -0.074 mmol/L per 100 µmol/L of teriflunomide. The therapeutic level for teriflunomide is in the range of 1–370 µmol/L[14].

Samples contaminated with benzalkonium salts used as coatings for in-dwelling lines may cause significant elevation of ionized calcium results[9]. For proper line-flushing procedures refer to CLSI H11[10].

Highly heparinized samples will decrease the iCa[6]; balanced heparin or low heparin collection tubes/syringes are recommended.

Systematic errors in ionized calcium readings may occur with over 20% hemodilution of plasma using solutions that are not consistent with the ionic characteristics of plasma, such as Normal Saline, Ringer's (Baxter Healthcare Corporation), and 10% Dextrose (Baxter Healthcare Corporation).

Hemodilution is associated with priming cardiopulmonary bypass pumps, plasma volume expansion, or other fluid administration therapies.

Such errors are prevented when physiologically balanced multi-electrolyte intravenous solutions containing low mobility anions that match the ionic characteristics of plasma, such as Plasma-Lyte™-A (Baxter Healthcare Corporation), Lactated Ringer's (Baxter Healthcare Corporation), Lactated Ringer's + 5% Dextrose injection (Baxter Healthcare Corporation), Plasbumin™-5 (Telacris Biotherapeutics), Pentaspan™ (Bristol-Myers Squibb), and Voluven™ (Fresenius Kabi) are used.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 0.4 mmol/L ascorbate, 1 mmol/L iodide, 2.2 mmol/L ibuprofen, 1.66 mmol/L acetaminophen, 2 mmol/L ammonium, 4 mmol/L lithium, 3 µmol/L dobutamine, 2.5 mmol/L tolbutamide, 1.34 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 0.7 mM metronidazole.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 20 mmol/L NaCl, 8 mmol/L KCl, 10 to 120 mmHg pCO_2, pH 6.9 to 7.7, +20 mmol/L bicarbonate, +20% PCV Hct, 0.8g/dL lipids, 9.1 mmol/L cholesterol, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

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12.9 Chloride (Cl-)

Chloride is measured by potentiometry using an ion selective membrane electrode. The concentration of chloride ions is obtained from the measured potential using the Nernst equation.

12.9.1 Indications for Use

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.

12.9.2 Contents

Each Test Card incorporating a chloride test contains a chloride ion sensing electrode with a chloride selective membrane, a reference electrode and a calibrator fluid containing a known concentration of chloride salts.

12.9.3 Traceability

Values of chloride ion concentration assigned to controls and calibrator fluids are traceable to NIST standards

12.9.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.9.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.9.6 Measurement Range

	Measurement Range	**Reference Range[1]**
Cl-	65 – 140 mmol/L	98 – 107 mmol/L
	65 – 140 mEq/L	98 – 107 mEq/L

12.9.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[2] for method comparison studies, CLSI EP07-A2[3] for interference studies, CLSI EP05-A2[4] for precision studies, and CLSI EP06-A[8] for linearity studies.

A. Precision Data

Precision (CLSI EP05-A2[4]): Three card lots using at least 25 epoc Readers with replicate measurements were run in-house twice a day for twenty days for each fluid. In the precision data tables below, SD_{WD} denotes within-day standard deviation, SD_{DD} denotes day-to-day standard deviation and SD_T denotes total standard deviation.

Aqueous Control	Units	N	Mean	SD_{WD}	SD_{DD}	SD_T	WD%CV	Total %CV
High level	mM	240	125.0	0.61	0.61	0.86	0.5%	0.7%
Low level	mM	240	76.9	0.35	0.18	0.39	0.5%	0.5%

Pooled Whole Blood Precision Data: One hundred forty five patient samples were run in duplicate with approximately equal numbers of venous, arterial and capillary samples. Pooled pair-wise precision was estimated over three concentration ranges.

Range	**<90**	**90 - 112**	**≥112**
N	20	98	27
Average Reading, mM	78	105	123
Pair Precision (SD), mM	0.4	0.7	1.2
%CV	0.5%	0.6%	1.0%

B. Linearity Data

Whole Blood Linearity Study (CLSI EP06-A[8]): This study was performed in-house on multiple whole blood samples with *Chloride* values spanning the reportable range. Linearity is reported versus theoretical chloride values based on gravimetric mixtures of high and low chloride samples (as measured using an in-house standard method). Six card lots were used in this study.

Test Range	Slope	Intercept	R
65-144mM	0.968	3.08	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[2]. In the method comparison statistics table, N is the number of patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Method comparison studies were performed at two hospitals. Venous samples were compared with 2 non-point-of-care systems (2 serum methods). Venous, arterial and capillary patient samples were compared with a whole blood point-of-care system.

Cl-	Non-POC Systems*	i-STAT 300†
N	95	155
Sxx	0.6	0.9
Syy	0.7	0.8
Slope	0.90	0.99
Intercept	9.62	0.07
Syx	2.2	1.9
Xmin	71	69
Xmax	142	139
R	0.97	0.99
Mean Bias at 112 mM	-1.4	-1.0

* Pooled venous sample data. Approximate equal number vs. Roche Cobas 6000[6], Siemens Advia[7]

† Patient samples approximately equal numbers of venous, arterial and capillary samples versus i-STAT 300[5]

D. Limitations and Interferences

Interference testing[3] was performed in-house on the epoc chloride sensor. In each of these tests a pooled human serum specimen was aliquoted into two (2) samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The chloride bias between the mean of six (6) replicates on both the control sample and the test sample with added interferent was calculated.

Unacceptable interference bias was defined as producing a significant error more than 5% of the time. 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 ≤ 3.5% for chloride concentrations ≤125 mM and ≤5.9% for chloride concentrations >125 mM.

Clinically significant interfering substances are itemized below:

- ß-Hydroxybutyrate will have no significant effect up to 8.27 mM (85.2 mg/dL) after which it will increase the chloride reading by up to 0.37 mM/mM β-hydroxybutyrate.
- Bromide will have no significant effect up to 1.63 mM (13.1 mg/dL) after which it will increase the chloride reading by up to 2.75 mM/mM bromide.
- Citrate will have no significant effect up to 2.79 mM (52.7 mg/dL) after which it will increase the chloride reading by up to 1.13 mM/mM citrate.
- N-acetylcysteine will have no significant effect up to 5.55 mM (90.5 mg/dL) after which it will decrease the chloride reading by up to 0.79 mM/mM N-acetylcysteine. It has been reported that 1 mM N-acetyl cysteine is therapeutically unattainable in plasma[9]. The therapeutic level for N-acetyl cysteine is 0.3 mM[10].
- Salicylic acid will have no significant effect up to 1.67 mM (22.9 mg/dL) after which it will increase the chloride reading by up to 2.94 mM/mM salicylic acid. Therapeutic range for salicylate is 0.1mM to 2 mM (1.4 mg/dL to 27.4 mg/dL)[11]
- Thiocyanate will have no significant effect up to 0.89 mM (5.2 mg/dL) after which it will increase the chloride reading by up to 5.62 mM/mM thiocyanate.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 1.324 mmol/L (20 mg/dL) acetaminophen, 3.62 mmol/L (65.2 mg/dL)

acetylsalicylic acid, 342 µmol/L (6.8 mg/dL) Na ascorbate, 3.4 µmol/L (0.1 mg/dL) EDTA, 71 µmol/L (1.7 mg/dL) methyldopa, 2.55 mmol/L (156 mg/dL) oxidized glutathione, 2.55 mmol/L (78 mg/dL) reduced glutathione, 920 µmol/L (6.96 mg/dL) hydroxyurea, 282 µmol/L (4 mg/dL) isoniazid (nydrazid), 0.8% (800 mg/dL) intralipid, 3 µmol/L (0.1 mg/dL) dobutamine, 5.87 µmol/L (0.1 mg/dL) dopamine, 86.8 mmol/L (400 mg/dL) ethanol, 105 µmol/L (0.44 mg/dL) fluoride, 133 µmol/L (0.4 mg/dL) formaldehyde, 55 mmol/L (990 mg/dL) glucose, 0.4 mmol/L (5 mg/dL) guaiacol, 3000 U/L heparin, 2.43 mmol/L (50 mg/dL) ibuprofen, 0.1 mmol/L (2.0 mg/dL) L-Dopa, 51.2 µmol/L (1.2 mg/dL) lidocaine, 248 µmol/L (6 mg/dL) thiopental, 2.37 mmol/L (64 mg/dL) tolbutamide, 2.99 mmol/L (38 mg/dL) iodide, 2.643 mmol/L (120 mg/dL) cefazolin, 1.46 mmol/L (81 mg/dL) ceftriaxone, (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: +342 µmol/L (+20.1mg/dL) bilirubin unconjugated, +342 µmol/L (+28.8 mg/dL) bilirubin conjugate, +382 µmol/L (+5.0 mg/dL) creatine, 109 mmHg CO_2, 15 mmHg $C0_2$, +40 mmol/L (+244 mg/dL) bicarbonate, pH > 8.0, pH < 6.8, +20% hematocrit, -20% hematocrit, <6% protein,>9% protein, 1.4 mmol/L (23.5 mg/dL) uric acid. 6.6 mmol/L (74 mg/dL) lactate, 131 mmHg O_2, 22 mmHg O_2, 0.25 mmol/L (2.9 mg/dL) proline, 1 µmol/L (0.01 mg/dL) sarcosine, 42.9 mmol/L (258 mg/dL) urea.

E. References

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12.10 Glucose (Glu)

Glucose is measured by amperometry[1]. The sensor comprises an immobilized enzyme first layer coated onto a gold electrode of the electrode module, with a diffusion barrier second layer. The glucose oxidase enzyme is employed to convert glucose to hydrogen peroxide,

$$\beta\text{-D-glucose} + O_2 + H_2O \xrightarrow{\text{Glucose Oxidase}} \text{D-gluconic acid} + H_2O_2 \quad (1)$$

and then uses an amperometric sensor to detect the enzymatically produced hydrogen peroxide. Peroxide detection is by redox mediated (ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt), horseradish peroxidase (HRP) catalyzed, reduction on a gold electrode.

$$H_2O_2 + HRP^{red} \rightarrow HRP^{ox} \quad (2)$$

$$HRP^{ox} + Red \rightarrow Ox + HRP^{red} \quad (3)$$

$$Ox + e^- \rightarrow Red \quad (4)$$

The reduction current is proportional to the concentration of glucose in the test fluid.

The epoc Glucose result is reported as **plasma equivalent[2]** glucose concentration**.**

12.10.1 Indications for Use

The Glucose 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.

Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, idiopathic hypoglycemia and of pancreatic islet cell tumors.

12.10.2 Contents

Each Test Card incorporating a Glucose test contains a sensing electrode with a redox mediated enzymatic membrane covered with an oxygen permeable diffusion layer, a reference electrode, a counter electrode and a calibrator fluid containing a known concentration of glucose.

12.10.3 Traceability

Glucose concentration values assigned to controls and calibrator fluids are traceable to NIST standards.

12.10.4 Sample Collection

Refer to 12.2.6 Sample Collection.

As per Tietz[13], capillary blood samples exhibit higher glucose than venous blood samples, by 2-5mg/dL in fasting patients and by 20% to 25% after a glucose load.

After the sample collection, glucose decreases in blood as a result of glycolysis by about 6% per hour[13], and by as much as 13% per hour[14]

Always test immediately using Li or Na heparin as the anticoagulant or using no anticoagulant.

Do not use NaF or potassium oxalate as preservative.

12.10.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.10.6 Measurement Range

	Measurement Range	Reference Range[3]
Glucose	1.1 – 38.5 mmol/L	4.1 – 5.5 mmol/L
	20 - 700 mg/dL	74 – 100 mg/dL
	0.20 -7.00 g/L	0.74 – 1.00 g/L

12.10.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[4] for method comparison studies, CLSI EP07-A2[5] for interference studies and CLSI EP05-A2[6] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	mg/dL	263.9	7.5	2.8
Low Level	mg/dL	44.2	1.5	3.4

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with *Glucose* values spanning the reportable range. Three types of samples were considered, i.e. normal hematocrit-normal venous blood pO_2, normal hematocrit– hypoxic blood sample and elevated hematocrit-normal venous blood pO_2. Linearity is reported versus two in-house standard whole blood glucose method with traceability to NIST standards.

Type of Blood Sample	Test Range	Units	Slope	Intercept	R
43% Hct, 30 mmHg pO_2	20 – 700	mg/dL	1.022	-3.32	0.9999
62% Hct, 30 mmHg pO_2	20 – 700	mg/dL	1.018	-4.04	0.9998
43% Hct, <20 mmHg pO_2	20 – 700	mg/dL	0.955	+0.33	0.9998

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[4]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study, the epoc System was compared with the i-STAT 300[7] in the lab and at one point-of-care site.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 CG8 cartridges test

Y: epoc test

Glu	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R
All	80	0.93	3.4	-2.2	1.031	5.6	20.0	605.5	0.9995

The precision in whole blood was assessed from the pooling of within method pairs from the method comparison data. This is shown in the table below.

Glucose [mg/dL]			
Range	20 – 70	70 – 200	200 – 700
N	10	59	11
Average Reading	44.8	116.4	383.8
Pair Precision (SD)	0.80	2.44	7.08
%CV	1.8%	2.1%	1.8%

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared simultaneously with the Roche-Hitachi[8] instrument in the lab and with i-STAT 300[7]. The summaries are presented in the tables below.

Method Comparison Summary Statistics: whole blood

X: Roche-Hitachi P800-D2400 test

Y: epoc test

Glu	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (%)
All	73	-	3.6	-0.2	0.971	3.0	23.0	546.0	0.998	-3.14

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 G cartridges test

Y: epoc test

Glu	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (%)
All	80	3.25	4.25	-1.33	1.003	4.45	22.5	517.5	0.999	-2.23%

The precision in whole blood was assessed from the pooling of within method pairs from the method comparison data. This is shown in the table below.

Glucose [mg/dL]			
Range	20 – 70	70 – 200	200 – 700
N	16	53	11
Average Reading	53.5	113.4	299.0
Pair Precision (SD)	1.32	3.18	8.73
%CV	2.47%	2.81%	2.92%

D. Consolidated Method Comparison Study Focusing on Low End Glucose Range

We evaluated the performance of the epoc glucose sensor in the low end range of glucose concentrations on Patient samples in clinical settings including at the point of care at several different hospitals. The results shown below include method comparison data against i-STAT[7] (whole blood method), ABL 800 Flex[9] (whole blood method), Roche-Hitachi[8] (plasma method), and J&J[12] (plasma method). We supplemented the above mentioned clinical results with an in-house full duplicate method comparison[4] against i-STAT[7] and ABL705[9]. In this study high hematocrit blood samples were prepared by removing half of the plasma volume from a venous sample that was allowed to glycolyse. The hematocrit of these specimens was tested by micro-centrifugation method[11] and found to be ~62%, i.e. characteristic to the upper range of the neonatal blood[10]. After the glucose reached ~20 mg/dL, it was spiked to cover uniformly the low range glucose, i.e. 20-80 mg/dL specific to neonatal population[10]. One sample was treated with Hexokinase, NADH-β and ATP in order to obtain a zero glucose concentration.

The data was processed as per CLSI EP09-A2 recommendations[4]. The correlation plot and bias plot are presented in the figures below. The test results versus the various reference instruments (X) are color coded.

epoc Low End Study	All points	Lab (plasma)	i-STAT	ABL	Roche	J&J
N	78	11	40	27	9	2
Sxx	1.0		0.6	1.6		
Syy	1.1	1.4	1.1	1.0	1.5	0.7
Intercept	-0.2	1.1	1.0	-2.2	0.8	
Slope	0.984	0.936	0.992	0.990	0.942	
Syx	2.9	2.1	2.55	2.16	2.21	
Xmin	1.5	23.0	20	1.5	23	25
Xmax	63.0	63.0	60	53	63	25
R	0.973	0.980	0.974	0.985	0.973	
Decision Level	40	40	40	40	40	
Bias	-0.8	-1.4	0.7	-2.6	-1.52	
Bias 95% Conf. Hi	-0.3	-0.5	1.3	-1.9	-0.18	
Bias 95% Conf. Lo	-1.3	-2.3	0.1	-3.3	-2.86	

Method Comparison Summary Statistics: whole blood

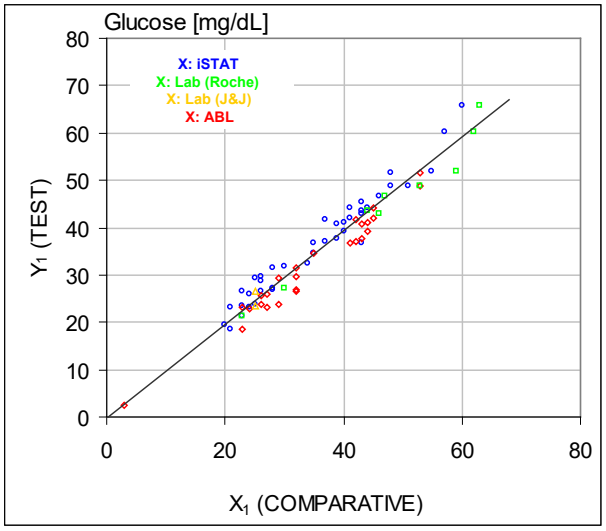
X (blue circles): i-Stat 300 G cartridges (whole blood) test

X (green squares): Roche Hitachi Lab (plasma) test

X (red diamonds): ABL 705 (whole blood) test

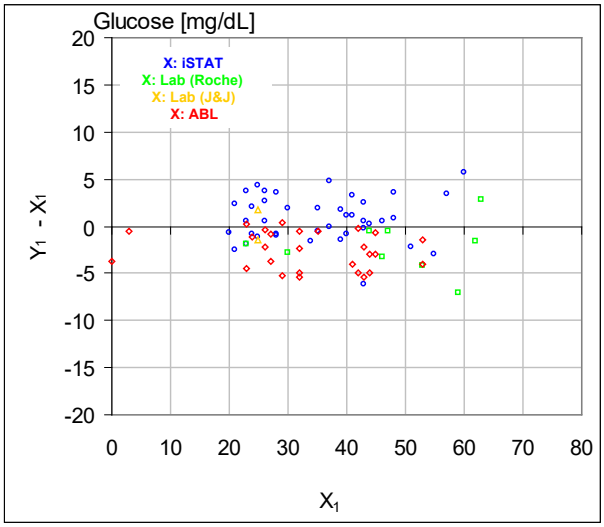
X (yellow triangles): J&J Lab (plasma) test

Y: epoc test



Low end glucose range, correlation plot versus various comparative instruments

Low end glucose range, bias plot versus various comparative instruments



E. Method Comparison Study Focusing on Capillary Blood Specimens

We evaluated the performance of the epoc tests on authentic capillary blood specimens in clinical settings at the point of care. The comparative method used i-STAT 300[7] analyzers with CG8 cartridges and Radiometer CLINITUBE capillaries. Comparison testing was performed at four (4) locations: NICU, Well-baby Nursery, and two (2) different outpatient drawing areas. There were a total of 48 samples collected, of which 24 in full duplicate. Of the 48 samples, 12 were adult blood specimens and 36 were neonatal blood specimens.

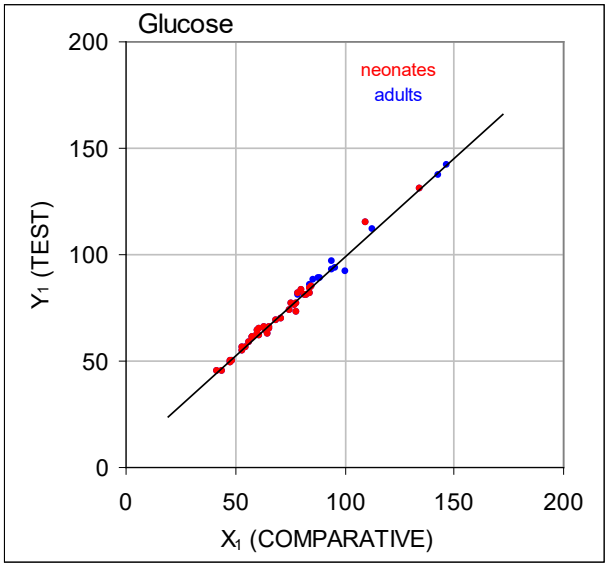
The data was processed as per CLSI EP09-A2 recommendations[4]. The correlation plot and bias plot are presented in the figures below. The test results versus the patient age are color coded.

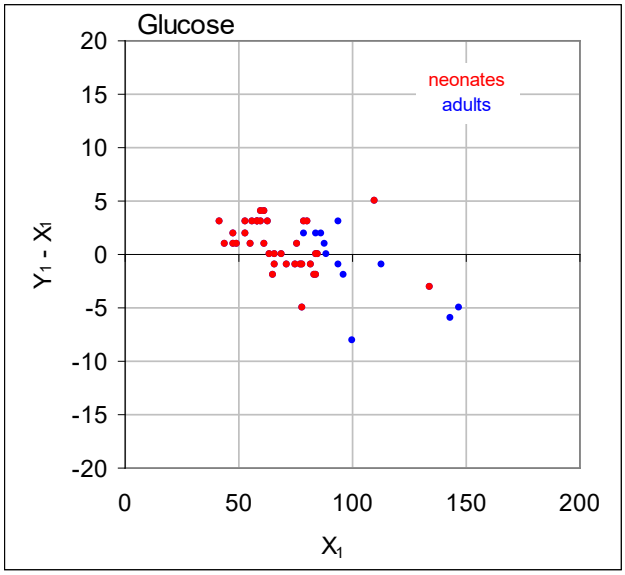
Method Comparison Summary Statistics: capillary blood

X: i-STAT 300 test

Y: epoc test

Glu	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R
All	48	1.13	1.80	5.1	0.935	2.42	42.5	147	0.9942





F. Limitations and Interferences

As per Tietz[13], capillary blood samples exhibit higher glucose than venous blood samples, by 2 to 5 mg/dL in fasting patients and by 20% to 25% after a glucose load.

After the sample collection, glucose decreases in blood as a result of glycolysis by about 6% per hour[13], and by as much as 13% per hour[14].

Always test immediately using Li or Na heparin as the anticoagulant or using no anticoagulant.

Do not use NaF or potassium oxalate as preservative.

Interference testing[5] was performed in-house on the epoc *glucose* sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The *glucose* bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Clinically significant interfering substances are itemized below:

- Iodide will have no significant effect up to 28 µM (0.47 mg/dL KI), after which it will decrease glucose reading by as much as (-0.16 mg/dL)/ µM I-, i.e. (-9.5 mg/dL)/(mg/dL KI).
- Bromide will have no significant effect up to 28 mM (224 mg/dL NaBr), after which it will decrease glucose reading by (-0.23 mg/dL)/mM Br, i.e. (-0.029 mg/dL)/(mg/dL NaBr).
- N-acetylcysteine will have no significant effect up to 500 µM (8.2 mg/dL) N-acetylcysteine, after which it will decrease the glucose reading by (-7.2mg/dL)/mM N-acetylcysteine, i.e. (-0.44mg/dL)/(mg/dL N-acetylcysteine). It has been reported that 1 mM N-acetylcysteine is therapeutically unattainable in plasma[15]. The therapeutical level for N-acetylcysteine is 0.3 mM[16].
- Flaxedil™ (gallamine triethiodide) will have no significant effect up to 11 µM (1 mg/dL), after which it will decrease the glucose reading by (–0.27 mg/dL)/ µM gallamine triethiodide, i.e. (–3 mg/dL)/(mg/dL gallamine triethiodide).
- Thiocyanate will have no significant effect up to 1 mM (5.9 mg/dL KSCN), after which it will decrease the glucose reading with -1.7%/mM SCN, i.e. (–0.29 mg/dL)/(mg/dL KSCN).
- Uric acid will have no significant effect up to 700µM (11.8 mg/dL), after which it will decrease the glucose reading by (-3.5 mg/dL)/mM uric acid, i.e. (–0.21 mg/dL)/(mg/dL uric acid).
- Mannose will have no significant effect up to 2 mM (36 mg/dL), after which it will increase the glucose reading by 2.12 mg/dL / (mM mannose), i.e. 0.059 mg/dL / (mg/dL mannose).
- Xylose will have no significant effect up to 3 mM (45 mg/dL), after which it will increase the glucose reading by 0.96 mg/dL / (mM xylose), i.e. 0.064mg/dL /(mg/dL xylose).
- Metamizole (dipyrone) will have no significant effect up to 0.194 mM, after which it will decrease the glucose reading by up to 3% / 0.1mM metamizole.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 1.66 mM (25 mg/dL) acetaminophen, 0.09 mmol/L (10 mg/dL) anidulafungin, 3.3 mmol/L (60 mg/dL) acetyl salicylate, 630 µmol/L (12.5 mg/dL) Na ascorbate, 89.2 µmol/L (4.5 mg/dL) clindamycin hydrochloride, 0.1 mmol/L (0.65 mg/dL) K cyanide, 6.15nmol/L (507 ng/dL) digoxin, 66 µmol/L (2.2 mg/dL) dobutamine, 100 µmol/L (1.9 mg/dL) dopamine HCl, 50 µmol/L (~1 mg/dL) L-dopa, 9 mmol/L (263 mg/dL) EDTA, 12 µmol/L (0.2 mg/dL) ephedrine, 87 mM (400 mg/dL) ethanol, 4.84 mmol/L (30 mg/dL) ethylene glycol, 1.78 µmol/L (60 µg/dL) famotidine, 1 mmol/L (18 mg/dL) fructose, 181 µmol/L (6 mg/dL) furosemide, 3.3 mmol/L (59 mg/dL) galactose, 238 µmol/L (10 mg/dL) gentamicin, 4.5 µmol/L (200 µg/dL) glipizide, 1.1 mmol/L (28.5 mg/dL) glucosamine, 2.55 mmol/L RBC oxidized glutathione, 2.55 mmol/L RBC reduced glutathione, 400 µmol/L (5 mg/dL) guaiacol, 80U/mL heparin, 0.4 mmol/L (14.5 mg/dL) hydrocortisone, 2.5 mmol/L (19 mg/dL) hydroxyurea, 292 µmol/L (4 mg/dL) Nydrazid™ (isoniazide), 48.6 µmol/L (1.76 mg/dL) levofloxacin, 1 mmol/L (34 mg/dL) linezolid, 13.3 mmol/L (479 mg/dL) maltose, 937.5 µmol/L (1500 mg/dL) icodextrin, 71 µmol/L (1.7 mg/dL) methyldopa, 77.4 µmol/L (2.9 mg/dL) 6α-methyl prednisolone, 0.7 mM (12 mg/dL) metronidazole, 17.4 µM (0.6 mg/dL) omeprazole, 102 µmol/L (2.4 mg/dL) procainamide, 4.22 µmol/L (0.12 mg/dL) promethazine hydrochloride, 37 µmol/L (1.2 mg/dL) quinidine, 1.67 µmol/L (40 µg/dL) salbutamol (albuterol), 4.34 mmol/L (60 mg/dL) salicylic acid, 1.96 µmol/L (60 µg/dL) sertraline, 413 µmol/L (10 mg/dL) sodium pentothal, 1 mmol/L (31 mg/dL) Tolinase™ (tolazamide), 2.37 mmol/L (64 mg/dL) tolbutamide, 69 µmol/L (10 mg/dL) vancomycin, 21.3 µmol/L (1 mg/dL) vitamin K1, 2.64 mmol/L (47 mg/dL) propofol, 0.7 mmol/L (334.2 mg/dL) cefotaxime, 0.16 mmol/L (59.4 mg/dL) ampicillin, 1 mmol/L (122.4 mg/dL) sodium perchlorate, 4.8 µM (1.75 mg/dL) Zofran™, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: +20 mmol/L (168 mg/dL) Na bicarbonate, +86 µmol/L (+7.3 mg/dL) bilirubin conjugated, +510 µmol/L (+30 mg/dL) bilirubin unconjugated, 13mM (503.1 mg/dL) cholesterol, 15 to 140 mmHg pCO_2, 2mmol/L (24mg/dL) L-cysteine, +20 mmol/L (+256 mg/dL) Na β-hydroxybutyrate, +20 mmol/L (+180 mg/dL) Na L-lactate, +0.8g/dL lipids, +59.2 µmol/L (+1.9 mg/dL) norepinephrine, pH 6.7 to 7.7, +20% PCV Hct, 3.4% to 10.4% total protein, 11.2mM (991 mg/dL) triglycerides.

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9. Radiometer ABL 705 and ABL 800Flex, Radiometer Medical ApS, Åkandevej 21, DK-2700 Brønshøj, Denmark, "Radiometer" and "ABL" are registered trademarks of Radiometer Medical ApS.
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12.11 Lactate (Lac)

Lactate is measured by amperometry[1]. The sensor comprises an immobilized enzyme first layer coated onto a gold electrode of the electrode module, with a diffusion barrier second layer. The lactate oxidase enzyme is employed to convert lactate to hydrogen peroxide,

$$\text{L-lactate} + O_2 + H_2O \xrightarrow{\text{Lactate Oxidase}} \text{Pyruvic acid} + H_2O_2 \quad (1)$$

and then uses an amperometric sensor to detect the enzymatically produced hydrogen peroxide. Peroxide detection is by redox mediated (ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt), horseradish peroxidase (HRP) catalyzed, reduction on a gold electrode.

$$H_2O_2 + HRP^{red} \rightarrow HRP^{ox} \quad (2)$$

$$HRP^{ox} + Red \rightarrow Ox + HRP^{red} \quad (3)$$

$$Ox + e^- \rightarrow Red \quad (4)$$

The reduction current is proportional to the concentration of lactate in the test fluid.

12.11.1 Indications for Use

The *Lactate* 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.

Lactate measurements are used to evaluate the acid-base status and are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity of the blood).

12.11.2 Contents

Each test card incorporating a *Lactate* test contains a sensing electrode with a redox mediated enzymatic membrane covered with an oxygen permeable diffusion layer, a reference electrode, a counter electrode and a calibrator fluid containing a known concentration of lactate.

12.11.3 Traceability

Certified standard reference material for lactate is not available at present. Lactate values assigned to controls and calibration verification materials are traceable to a working calibrator prepared from Sodium L-Lactate from Sigma-Aldrich Co., Item Number 71718, >99% purity.

12.11.4 Sample Collection

Refer to 12.2.6 Sample Collection.

Collection of a satisfactory specimen for Lactate analysis requires special procedures to prevent changes in lactate both during and after blood is drawn[11].

As per Tietz[11], for venous samples, do not use a tourniquet or immediately remove the tourniquet before the draw. During exercise, Lactate may increase significantly within 10 seconds. Therefore, for relevant Lactate readings, the patients should be fasting and at rest for at least 2 hours. After sample collection, lactate rapidly increases in blood as a result of glycolysis by as much as 20% in 3 min and 70% in 30 min at 25°C.

Always test immediately using Li or Na heparin as the anticoagulant or using no anticoagulant. Do not use NaF or potassium oxalate as preservative.

12.11.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.11.6 Measurement Range

	Measurement Range	**Reference Range[2], Arterial**	**Reference Range[2], Venous**
Lactate	0.30 – 20.00 mmol/L	0.36 – 0.75 mmol/L	0.56 – 1.39 mmol/L
	2.7 – 180.2 mg/dL	3.2 – 6.8 mg/dL	5.0 – 12.5 mg/dL
	0.03 – 1.80 g/L	0.03 – 0.07 g/L	0.05 – 0.12 g/L

12.11.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[3] for method comparison studies, CLSI EP07-A2[4] for interference studies, CLSI EP06-A[7] for linearity studies, and CLSI EP05-A2[5] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	**Units**	**Mean**	**SD**	**%CV**
High Level	mmol/L	6.11	0.21	3.4
Low Level	mmol/L	0.95	0.06	6.3

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

Whole Blood Linearity Study (CLSI EP06-A[7]): This study was performed in-house on multiple whole blood samples with *Lactate* values spanning the reportable range. Linearity is reported versus theoretical lactate values based on gravimetric mixtures of high and low lactate samples. Four (4) card lots were used in this study.

Test Range	**Slope**	**Intercept**	**R**
0.3-20.1 mM	1.001	0.271	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[3]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Method comparison studies were performed at two (2) hospitals. At one hospital, 99 venous samples were tested. At another hospital, both 43 arterial and 44 capillary samples were tested. Sample lactate concentrations on the comparison device varied from 0.57 to 14.57 mmol/L.

In these studies, the epoc System was compared with the i-STAT 300 analyzer[6].

Method Comparison Summary Statistics: whole blood—venous, arterial, capillary

X: i-STAT CG4+ cartridges

Y: epoc test

Lac	epoc	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (%)
	i-STAT	373	0.215	0.530	0.132	0.967	0.948	0.48	19.95	0.985	2.75

D. Limitations and Interferences

Collection of satisfactory specimen for Lactate analysis requires special procedures to prevent changes in Lactate both during and after blood is drawn[11].

As per Tietz[11], for venous samples, do not use a tourniquet or immediately remove the tourniquet before the draw. During exercise, Lactate may increase significantly within 10 seconds. Therefore, for relevant Lactate readings, the patients should be fasting and at rest for at least 2 hours.

After the sample collection, lactate rapidly increases in blood as a result of glycolysis by as much as 20% in 3 min and 70% in 30 min at 25°C.

Always test immediately using Li or Na heparin as the anticoagulant or using no anticoagulant.

Do not use NaF or potassium oxalate as preservative.

Interference testing[4] was performed in-house on the epoc lactate sensor. In each of these tests a pooled human serum specimen was aliquoted into two (2) samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The lactate bias between the mean of six (6) replicates on both the control sample and the test sample with added interferent was calculated.

Unacceptable interference bias was defined as producing a significant error more than 5% of the time.

Significant interfering substances are itemized below:

- Acetaminophen will have no significant effect up to 0.81 mM after which it will increase the lactate reading up to 306µM/mM Tylenol™ (acetaminophen). Because the therapeutic upper limit for acetaminophen is 0.20 mM, interfering levels of acetaminophen should only be encountered in overdose situations
- Iodide will decrease the lactate reading up to -3.3 mM/mM of Iodide for an Iodide concentration under 0.3 mM. Above 0.3 mM Iodide, the Lactate bias will be a constant -1.0 mM.
- Bromide will have no significant effect up to 25.4 mM after which it will decrease the lactate reading up to 14.6µM/mM Bromide.
- Thiocyanate will have no significant effect up to 2.7 mM after which it will decrease the lactate reading by up to 96.6µM/mM thiocyanate.
- N-acetylcysteine will have no significant effect up to 3.7 mM after which it will decrease the lactate reading by up to 96.3µM/mM N-acetylcysteine. It has been reported that 1 mM N-acetylcysteine is therapeutically unattainable in plasma[9]. The therapeutical level for N-acetylcysteine is 0.3 mM[10].

Ethylene glycol ingestion and metabolism has been shown to produce falsely elevated lactate measurements[8]. Ethylene glycol plus three metabolism products - Glycolic Acid, Glyoxylic Acid and Oxalic Acid - were tested for interference. Ethylene Glycol and Oxalic Acid do not interfere significantly.

- Glycolic Acid will have no significant effect up to 0.87 mM after which it will increase the lactate reading up to 142µM/mM glycolic acid.
- Glyoxylic Acid will have no significant effect up to 0.85 mM after which it will increase the lactate reading up to 373µM/mM glyoxylic acid.

The following levels of exogenous interferences were tested and found to be insignificant: 630µmol/L (12.5 mg/dL) Na ascorbate, 20 mmol/L (588 mg/dL) citrate, 100µmol/L (~2 mg/dL) L-dopa, 9 mmol/L (263 mg/dL) EDTA, 4.84 mmol/L (30 mg/dL) ethylene glycol, 105µmol/L (0.441 mg/dL) Na fluoride, 71µmol/L methyldopa, 2.55 mmol/L oxidized glutathione, 2.55 mmol/L reduced glutathione, 132µmol/L (1.0 mg/dL) hydroxyurea, 292µmol/L (4 mg/dL) Nydrazid™ (isoniazide), 81µmol/L (1.5 mg/dL) K oxalate, 0.037 mmol/L (1.2 mg/dL) quinidine, 2.64 mmol/L (47 mg/dL) propofol, 0.7 mmol/L (334.2 mg/dL) cefotaxime, 0.16 mmol/L (59.4 mg/dL) ampicillin, 1 mmol/L (122.4 mg/dL) sodium perchlorate, 3.7 mmol/L (603.8 mg/dL) N-acetylcysteine, 4.8 µM Zofran™, 0.7 mM metronidazole, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be insignificant: +342µmol/L (+29.0 mg/dL) bilirubin conjugated, +342µmol/L (+20.1 mg/dL) bilirubin unconjugated, +13 mmol/L (+503.1 mg/dL) cholesterol, 2mmol/L (24mg/dL) L-cysteine, +0.8g/dL lipids, pH (+0.4, -0.4), 3% to 10% total protein, 1.4 mM (+ 23.5 mg/dL) Uric Acid. Low hematocrit did not interfere down to a level of 21 % hematocrit and high hematocrit did not interfere up to a level of 61 % hematocrit. Triglycerides did not show significant interference up to a level of 37 mM (3274 mg/dL). pO_2 partial pressures below 20 mmHg (2.67kPa) may decrease lactate values.

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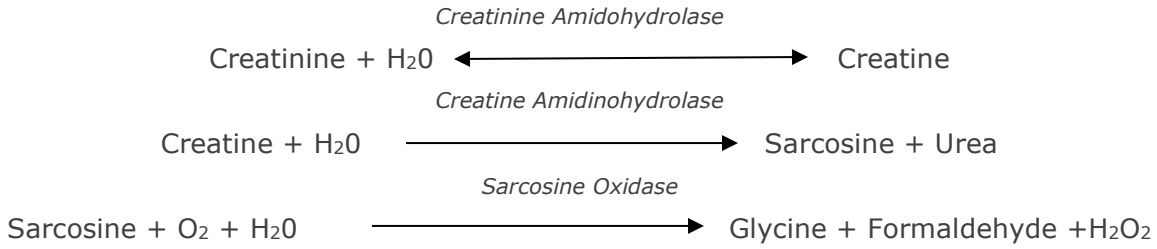
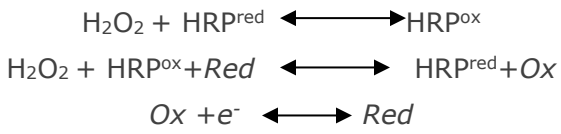
12.12 Creatinine (Crea)

Creatinine is measured by amperometry[1]. Each creatinine sensor is a three layer enzyme electrode, comprising a first immobilized enzyme creatinine-conversion underlayer coated onto a gold electrode, a second immobilized enzyme creatine-screening layer and a third diffusion barrier layer.

The creatinine electrode underlayer contains the enzymes Creatinine Amidohydrolase, Creatine Amidinohydrolase and Sarcosine Oxidase which convert creatinine to hydrogen peroxide in an enzyme → product cascade,



and then uses the underlying gold electrode to detect the enzymatically produced hydrogen peroxide. Peroxide detection is by redox-mediated horseradish-peroxidase (HRP)-catalyzed reduction.



The reduction current is proportional to the concentration of creatinine in the test fluid.

12.12.1 Indications 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.

12.12.2 Contents

Each test card incorporating a Creatinine test contains a sensing electrode with redox mediated enzymatic membrane layers covered with an oxygen permeable diffusion layer, a reference electrode, a counter electrode and a calibrator fluid containing a known concentration of creatinine.

12.12.3 Traceability

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

12.12.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.12.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.12.6 Measurement Range

	Measurement Range	**Reference Range[2,9]**
Creatinine	0.30 – 15.00 mg/dL	0.51 – 1.19 mg/dL
	27 – 1326 μmol/L	45 – 105 μmol/L

12.12.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[3] for method comparison studies, CLSI EP07-A2[4] for interference studies, CLSI EP06-A2[7] for linearity studies, and CLSI EP05-A2[5] for precision studies.

A. Precision Data

Precision (CLSI EP05-A2[5]): Three card lots card lots using at least 25 epoc Readers with replicate measurements were run in-house twice a day for twenty days for each fluid. In the precision data tables below, SD_{WD} denotes within-day standard deviation, SD_{DD} denotes day-to-day standard deviation and SD_T denotes total standard deviation.

Aqueous Control	**Units**	**N**	**Mean**	**SD_{WD}**	**SD_{DD}**	**SD_T**	**WD%CV**	**Total %CV**
High Level	mg/dL	241	5.50	0.197	0.112	0.226	3.6%	4.1%
Low Level	mg/dL	239	0.71	0.030	0.017	0.035	4.2%	4.9%

Pooled Whole Blood Precision Data: One hundred twenty seven patient samples were run in duplicate with approximately equal numbers of venous, arterial and capillary samples. Pooled pair-wise precision was estimated over three concentration ranges.

Range	**≤2**	**2 – 10**	**>10**
N	88	44	22
Average Reading, mg/dL	0.74	5.96	13.40
Pair Precision (SD), mg/dL	0.05	0.28	0.67
%CV	6.4%	4.6%	5.0%

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

Whole Blood Linearity Study (CLSI EP06-A[7]): This study was performed in-house on multiple whole blood samples with *Creatinine* values spanning the reportable range. Linearity is reported versus theoretical creatinine values based on gravimetric mixtures of high and low creatinine samples (as measured using an in-house standard whole blood creatinine method with IDMS traceability). Three card lots were used in this study.

Test Range	Slope	Intercept	R
0.251 – 15.5 mg/dL	1.00	0.07	0.995

C. Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[3]. In the method comparison statistics table, N is the number of patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Venous, arterial and capillary patient samples were compared with an IDMS-traceable serum-based laboratory system.

Crea	**Roche Cobas 6000[10]**
N	144*
Sxx	0.10
Syy	0.30
Slope	1.03
Intercept	-0.10
Syx	0.45
Xmin	0.30
Xmax	14.80
R	0.995
Mean Bias in eGFR Range of Interest (1.00–1.50 mg/dL)	-0.06

*Patient samples: approximately equal numbers of venous, arterial, and capillary samples

D. Limitations and Interferences

Interference testing[4] was performed in-house on the epoc creatinine sensor. In each of these tests a pooled human serum specimen was aliquoted into two (2) samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The creatinine bias between the mean of six (6) replicates on both the control sample and the test sample with added interferent was calculated.

Unacceptable interference bias was defined as producing a significant error more than 5% of the time. 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 ≤ 0.23 mg/dL for creatinine concentrations ≤2 mg/dL and ≤6.8% for creatinine concentrations >2 mg/dL.

Clinically significant interfering substances are itemized below:

- Creatine will have no significant effect up to 0.10 mmol/L (1.34 mg/dL) after which it will increase the creatinine concentration by up to 2.17 mg/dL creatinine per mmol/L creatine. The reference range of creatine in plasma is 8 – 31 µmol/L (0.1-0.4 mg/dL) in males and 15 – 53 µmol/L (0.2 – 0.7 mg/dL) in females[11].
- Iodide will have no significant effect up to 0.45 mmol/L (5.74 mg/dL) after which it will decrease the creatinine concentration by up to 0.49 mg/dL creatinine per mmol/L iodide.
- N-acetyl cysteine will have no significant effect up to 0.47 mmol/L (7.70 mg/dL) after which it will decrease the creatinine concentration by up to 0.72 mg/dL creatinine per mmol/L N-acetyl cysteine. It has been reported that 1 mM N-acetyl cysteine is therapeutically unattainable in plasma[8]. The therapeutic level for N-acetyl cysteine is 0.3 mM[12].

Ethylene glycol plus three metabolism products - Glycolic Acid, Glyoxylic Acid and Oxalic Acid - were tested for interference. Ethylene glycol, glyoxylic acid, and oxalic acid do not interfere significantly with epoc creatinine.

- Glycolic acid will have no significant effect up to 1.69 mM, after which it will decrease the creatinine reading by up to 5% / 1 mM glycolic acid.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 1.324 mmol/L (20 mg/dL) acetaminophen, 3.62 mmol/L (65.2 mg/dL) acetylsalicylic acid, 342 µmol/L (6.8 mg/dL) Na ascorbate, 3.4 µmol/L (0.1 mg/dL) EDTA, 71 µmol/L (1.7 mg/dL) methyldopa, 2.55 mmol/L (156 mg/dL) oxidized glutathione, 2.55 mmol/L (78 mg/dL) reduced glutathione, 920 µmol/L (6.96 mg/dL) hydroxyurea, 282 µmol/L (4mg/dL) isoniazid (nydrazid), 0.8% (800 mg/dL) intralipid, 3 µmol/L (0.1 mg/dL) dobutamine, 5.87 µmol/L (0.1 mg/dL) dopamine, 86.8 mmol/L (400 mg/dL) ethanol, 105 µmol/L (0.44 mg/dL) fluoride, 133 µmol/L (0.4 mg/dL) formaldehyde, 55 mmol/L (990 mg/dL) glucose, 0.4 mmol/L (5 mg/dL) guaiacol, 3000 U/L heparin, 2.43 mmol/L (50 mg/dL) ibuprofen, 0.1 mmol/L (2.0 mg/dL) L-Dopa, 51.2 µmol/L (1.2 mg/dL) lidocaine, 248 µmol/L (6 mg/dL) thiopental, 2.37 mmol/L (64 mg/dL) tolbutamide, 2.643 mmol/L (120 mg/dL) cefazolin, 1.46 mmol/L (81 mg/dL) ceftriaxone, 4.34 mmol/L (70 mg/dL) salicylate, 6.88 mmol/L (40 mg/dL) thiocyanate, 10 mmol/L (104 mg/dL) β-hydroxybutyrate, 37.5 mmol/L (300 mg/dL) bromide, 20 mmol/L (384 mg/dL) Na citrate, 78.1 µmol/L (6.4 mg/dL) rifampicin, 5 µmol/L (0.7 mg/dL) bacitracin, 30.2 µmol/L (1 mg/dL) ciprofloxacin, 48.6 µmol/L (1.8 mg/dL) levofloxacin, 2.4 µmol/L (0.08 mg/dL) norfloxacin, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: +342 µmol/L (+20.1mg/dL) bilirubin unconjugated, +342 µmol/L (+28.8 mg/dL) bilirubin conjugate, 109 mmHg CO_2, 15 mmHg $C0_2$, +40 mmol/L (+244 mg/dL) bicarbonate , pH >8.0, pH < 6.8, Hct<10PCV, Hct>75PCV, <6% protein, >9% protein, 1.4 mmol/L (23.5 mg/dL) uric acid. 6.6 mmol/L (74 mg/dL) lactate, 131 mmHg O_2, 22 mmHg O_2, 0.25 mmol/L (2.9 mg/dL) proline, 1 µmol/L (0.01 mg/dL) sarcosine, 42.9 mmol/L (258 mg/dL) urea.

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12.13 Hematocrit (Hct)

Hematocrit is measured by AC conductometry using two (2) gold electrodes. The conductance of the blood sample in the fluidic path between the two (2) electrodes, after correction for variable plasma conductivity through the measurement of sodium concentration, is inversely proportional to the hematocrit value.

12.13.1 Indications for Use

The Hct 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.

Measurement of Hct distinguishes normal from abnormal states of blood volume, such as anemia and erythrocytosis.

12.13.2 Contents

Each Test Card incorporating an Hct test contains two (2) gold sensing electrodes and a calibrator fluid containing a known concentration of dissolved electrolytes with a known conductivity.

12.13.3 Traceability

Hematocrit values assigned to controls and calibrator fluids are traceable to the standard method for measuring packed cell volume by the microhematocrit method, using whole blood with K_3EDTA anticoagulant, – applicable standard CLSI H07-A3[1].

12.13.4 Sample Collection

Refer to 12.2.6 Sample Collection.

12.13.5 Additional Information

Refer to Section 3 "epoc System Operation" in this manual for detailed sample collection and system operating instructions for conducting a blood test.

Refer to Section 9 "Quality Assurance" in this manual for quality control requirements.

12.13.6 Measurement Range

	Measurement Range	**Reference Range[2]**
Hct	10 – 75%	38 – 51%
	0.10 – 0.75	0.38 – 0.51 L/L

12.13.7 Performance Data

Typical performance data summarized below were obtained in-house as well as in healthcare facilities by healthcare professionals trained in the use of the epoc System. Experimental designs conformed to applicable CLSI guidelines.

Applicable standards include: CLSI EP09-A2[3] for method comparison studies, CLSI EP07-A2[4] for interference studies and CLSI EP05-A2[7] for precision studies.

A. Precision Data

Twenty replicates of each of two levels of commercial controls were analyzed at each of 20 different sites. The precision study at each site employed from two (2) to eight (8) epoc Readers, and multiple lots of epoc Test cards were included across all of the sites. The pooled SD and averaged means are presented below:

Aqueous Control	Units	Mean	SD	%CV
High Level	% PCV	43.9	0.7	1.6
Low Level	% PCV	22.7	0.5	2.2

Because the SDs presented here are the pooled averages from multiple customer performance verifications, it is expected that, occasionally, SDs from an individual precision study to be higher or lower than these averages. Each site must establish whether the results of their precision studies are clinically acceptable. Alternatively, an f-test can be used to determine whether their precision is statistically equivalent to typical precision values summarized above.

B. Linearity Data

This study was performed in-house on multiple whole blood samples with hematocrit level spanning the reportable range. Linearity is reported versus an in-house standard spun hematocrit method.

	Test Range	Units	Slope	Intercept	R
Hct	0 – 75	% PCV	1.005	-0.58	0.9995

C. Clinical Sites Method Comparison Data

Linear regression analysis was performed on the method comparison data in accordance with CLSI EP09-A2[3]. In the method comparison statistics table, N is the number of Patient specimens in the data set, Sxx and Syy are the pooled pair-wise imprecision of the comparative and epoc test methods respectively, Syx is the standard error and R is the correlation coefficient.

Clinical Site Method Comparison 1: In one hospital study the epoc System was compared with the i-STAT 300[5] in the lab (two test occasions), and then at three (3) point-of-care sites.

Method Comparison Summary Statistics: whole blood

X: i-STAT 300 test

Y: epoc test

Hct	Lab 1	Lab 2	POC 1	POC 2	POC 3	All
N	34	23	35	28	22	142
Sxx	0.49	0.66	0.46	0.67	0.69	0.58
Syy	0.69	0.42	0.65	0.57	0.80	0.64
Intercept	-1.5	1.3	0.0	-0.4	-0.4	-1.1
Slope	1.086	1.006	1.034	1.027	1.051	1.066
Syx	1.28	1.17	1.05	1.48	1.82	1.36
Xmin	19	24	28	23	24	19
Xmax	73	57	41	39	60	73
R	0.995	0.990	0.964	0.955	0.976	0.987
Mean Bias (%CV)						1.7

Clinical Site Method Comparison 2: In another hospital study, the epoc System was compared with the Radiometer ABL 735[6] in the lab. (The ABL 735 hematocrit value was calculated from the measured hemoglobin.)

Method Comparison Summary Statistics: whole blood

X: Radiometer ABL 735

Y: epoc test

Hct	N	Sxx	Syy	Intercept	Slope	Syx	Xmin	Xmax	R	Mean Bias (%CV)
Lab	77	1.42	1.16	-2.3	1.006	2.84	21	63	0.964	-1.6

D. Limitations and Interferences

Blood samples must be well mixed in order to obtain accurate hematocrit results. The best way to ensure this is to test the sample immediately after collection. For samples where testing delays of greater than one minute occur, cells should be thoroughly re-mixed by rolling the sample between the hands for several rotations in both directions.

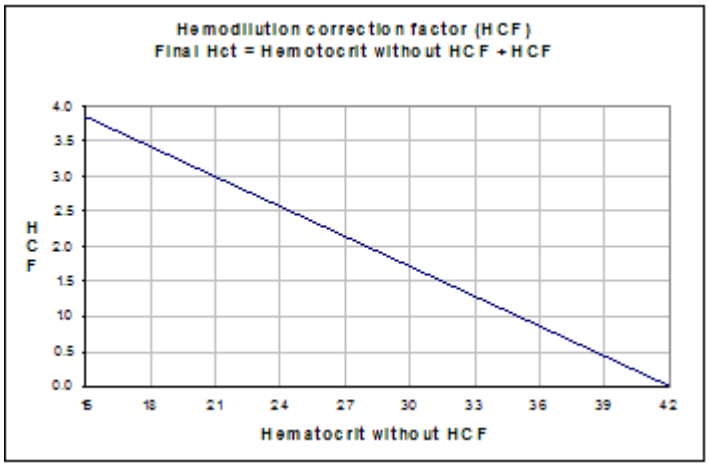
Note: Thin diameter collection devices (for example, 1cc syringes or epoc Care-Fill Capillary Tubes) may be difficult to re-mix. Therefore, it is recommended that testing from these devices not be delayed. Refer to 12.2.6 Sample Collection.

Interference testing[4] was performed in-house on the epoc hematocrit sensor. In each of these tests a whole blood specimen was aliquoted into two samples. The test sample was spiked by addition of interferent, while the control sample was spiked by the addition of the solvent of the interferent. The hematocrit bias between the mean of six replicates on both the control sample and the test sample with added interferent was calculated.

Note: Automated hematology analyzers may underestimate or overestimate hematocrit values due to the differing osmotic effects on RBC in the isotonic buffer matrix, compared to their native plasma matrix[8].

Clinically significant interfering substances are itemized below:

- Total protein content will affect the hematocrit results as follows: an increase (decrease) of 1 g/dL of total protein will increase (decrease) the hematocrit value by approximately 1% PCV. Total protein levels vary with the clinical populations[2]. Low total protein values may be found in neonates, burned Patients, Patients receiving large volumes of IV fluids, and Patients undergoing cardiopulmonary bypass (CPB) and extra-corporeal membrane oxygenation (ECMO). For the case of hemodilution, the user should activate the hemodilution correction factor or "HCF" in the epoc Host (see Section 6 "epoc Host" and Section 7 "epoc Host Administration" in this manual for details). The HCF corrects hematocrit for low protein in blood samples known to be diluted with fluids that do not contain protein. There is no HCF applied for Hct over 42%. It is recommended that each practice verify the use of the HCF algorithm as well as the time interval that the HCF should be selected during the recovery period.



- A significant increase in white blood cell count may increase the hematocrit result.
- Abnormally high lipids may increase hematocrit results.

The following levels of exogenous interferences were tested and found to be clinically insignificant: 447 mg/dL ethanol, 1 mmol/L sodium pentothal, 4.3 mmol/L acetyl salicylate, 0.4 mmol/L ascorbate, 4.3 mmol/L salicylate, 1 mmol/L iodide, 2.2 mmol/L ibuprofen, 4 mmol/L lithium, 19 mmol/L bromide, 2.64 mmol/L propofol, 0.7 mmol/L cefotaxime, 0.16 mmol/L ampicillin, 1 mmol/L sodium perchlorate, 4.8 µM Zofran™, 2.5 mM N-acetylcysteine, 0.7 mM metronidazole, 719 µmol/L (19.2 mg/dL) leflunomide, 1002 µmol/L (26.9 mg/dL) teriflunomide.

The following levels of endogenous interferences were tested and found to be clinically insignificant: 0.8g/dL lipids, 9.1 mmol/L cholesterol, 20 mmol/L β-hydroxybutyrate, 2mmol/L (24mg/dL) L-cysteine, 0.26 mmol/L bilirubin, +2 mmol/L phosphate.

E. References

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12.14 Calculated Values

Note: Except where noted, calculated values are only available when the measured parameters from which they are derived are displayed.

12.14.1 Calculated Bicarbonate ($cHCO_3$-), Calculated Total Carbon Dioxide ($cTCO_2$), Base Excess (BE)[1]

*Note: Alternate analyte acronyms for **$cHCO_3$-** are **HCO_3-act** or **HCO_3-.***

Calculated bicarbonate: LOG $cHCO_3$- = pH + LOG pCO_2 – 7.608

Calculated TCO_2: $cTCO_2$ = $cHCO_3$- + 0.0307 x pCO_2

Base Excess (extra cellular fluid): BE(ecf) = $cHCO_3$- – 24.8 + 16.2 x (pH – 7.4)

Base Excess (blood): BE(b) = (1 – 0.014 x cHgb) x ($cHCO_3$- – 24.8 + (1.43 x cHgb + 7.7) x (pH – 7.4)) *

Applicable standards: CLSI C46-A2[1]. In above equations, units are mmHg for pCO_2 and g/dL for cHgb.

* cHgb is obtained from measured Hematocrit value, even if Hematocrit and cHgb are not displayed.

Measurement Range

	Units of Measure	Measurement Range	Reference Range[8-10]	
			Arterial	Venous
$cHCO_3$-	mmol/L	1 – 85	21 – 28	22 – 29
	mEq/L			
$cTCO_2$	mmol/L	5 – 50	22 – 29	23 – 30
	mEq/L			
BE(ecf)	mmol/L	-30 – +30	-2 – +3	-2 – +3
	mEq/L			
BE(b)	mmol/L	-30 – +30	-2 – +3	-2 – +3
	mEq/L			

12.14.2 Calculated Oxygen Saturation (cSO_2)[2]

*Note: Alternate analyte acronym for **cSO_2** is **O2SAT**.*

$cSO_2 = 100(X^3 + 150X) / (X^3 + 150X + 23400)$

$X = pO_2 \times 10^{(0.48(pH-7.4)-0.0013(cHCO_3-25))}$

Measurement Range

	Measurement Range	Reference Range, Arterial
cSO_2	0 – 100%	94 – 98%

Because oxygen saturation also depends on the effects of 2,3 diphosphoglycerate and dysfunctional hemoglobins (carboxy-, met–, and sulfhemoglobin) in blood, the above equation does not account for variations in these values, the oxygen saturation that is reported should only be used as an estimate of the actual value[1,3,11]. Shifts in the oxyhemoglobin dissociation curve have also been recorded in cases of uremic and diabetic coma, as well as pernicious anemia[10]. Clinically significant errors can result from incorporation of such an estimated value for oxygen saturation in further calculations, such

as shunt fraction, or by assuming the value obtained is equivalent with fractional oxyhemoglobin.

Oxygen saturation is a useful predictor of the amount of oxygen that is available for tissue perfusion. Some causes for decreased values of cSO_2 include low pO_2 or impaired ability of hemoglobin to carry oxygen.

12.14.3 Anion Gap (AGap)[8]

Anion Gap: AGap = (Na+) - (Cl- + $cHCO_3$-)

Anion Gap, K: AGapK = (Na+ + K+) - (Cl- + $cHCO_3$-)

Applicable reference: Tietz 2nd ed.[8].

Measurement Range

	Units of Measure	Measurement Range	Reference Range
AGap	mmol/L	-14-+95	7-16
	mEq/L		
AGapK	mmol/L	-10-+99	10-20
	mEq/L		

12.14.4 Estimated Glomerular Filtration Rate (GFR)

When Crea measurement is available on the Test Card and enabled by the system administrator for testing, the following Estimated Glomerular Filtration Rate (GFR) values may be calculated: ***GFRmdr, GFRmdr-a, GFRckd, GFRckd-a, GFRswz***. These values are estimated using different methods and can all be reported on the epoc System.

Note: In earlier epoc System software versions, the only values for Estimated Glomerular Filtration Rate were MDRD type. They were shown in test results as simply "eGFR" and "eGFR-a." With more Estimated Glomerular Filtration Rate options available, new notations have been introduced: GFRmdr, GFRmdr-a, GFRckd, GFRckd-a, GFRswz.

Estimated Glomerular Filtration Rate (IDMS-traceable MDRD type):

$GFRmdr^{4,5} = 175 \times (Crea^{-1.154}) \times (Age^{-0.203}) \times$ (0.742 if female, 1 if male)

Note: Formerly, GFRmdr was named eGFR.

Estimated Glomerular Filtration Rate (IDMS-traceable MDRD type)*, if African American*:

$GFRmdr\text{-}a^{4,5} = 175 \times (Crea^{-1.154}) \times (Age^{-0.203}) \times$ (0.742 if female, 1 if male) x 1.212

Note: Formerly, GFRmdr-a was named eGFR-a.

Estimated Glomerular Filtration Rate (CKD-EPI equation):

$GFRckd^{12\text{-}17} = 141 \times \min(Crea/\kappa, 1)^{\alpha} \times \max(Crea/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ (1.018 if female, 1 if male)

Estimated Glomerular Filtration Rate (CKD-EPI equation)*, if African American*:

$GFRckd\text{-}a^{12\text{-}17} = 141 \times \min(Crea/\kappa, 1)^{\alpha} \times \max(Crea/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ (1.018 if female, 1 if male) x 1.159

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of Crea/κ or 1

max = indicates the maximum of Crea/κ or 1

Estimated Glomerular Filtration Rate (Bedside Schwartz equation), *for use in children 1-18 years old*:

$GFRswz^{18\text{-}20}$ = 0.413 x (height/Crea)

Crea concentration is in units of mg/dL.

Age (years) and gender (male or female) are user inputs.

Height is expressed in centimeters, also a user input.

Age Range

	Age Range	Note
GFRmdr, GFRmdr-a	18 - 120	GFRmdr, GFRmdr-a values are not reported if Age is less that 18 years old or greater than 120 years old.
GFRckd, GFRckd-a	19 - 120	GFRckd, GFRckd-a values are not reported if Age is less that 19 years old or greater than 120 years old.
GFRswz	1 - 18	GFRswz values are not reported if Age is less that 1 year old or greater than 18 years old.

Measurement Range

	Measurement Range	Reference Range
GFRmdr, GFRmdr-a	2 – 60 or >60 mL/min/1.73m^2 *	†
GFRckd, GFRckd-a	1 – 225 mL/min/1.73m^2	†
GFRswz	1 – 275 mL/min/1.73m^2	†

***** *Numeric values will be reported for values between 2-60 mL/min/1.73 m^2. Values >60 will be reported as > 60 mL/min/1.73 m^2. This range is based on the specific National Kidney Disease Education Program (NKDEP) recommendation for reporting GFRmdr values[4]. GFRmdr > 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.*

† Widely accepted reference ranges are not well established for Estimated Glomerular Filtration Rate. Institutions should establish and set their own reference range values.

12.14.5 Calculated Hemoglobin (cHgb)[6,7]

Hemoglobin concentration is calculated from the measured hematocrit according to the relation:

cHgb (g/dL) = Hct (decimal fraction) x 34

The relation above assumes a normal Mean Corpuscular Hemoglobin Concentration, MCHC of 34%[6,7].

Measurement Range

	Measurement Range	Reference Range
cHgb	3.3 – 25 g/dL	12 – 17 g/dL
	2.0 – 15.5 mmol/L	7.4 – 10.6 mmol/L
	33 – 250 g/L	120 – 170 g/L

12.14.6 Alveolar Oxygen (A), Arterial Alveolar Oxygen Tension Gradient (A-a), Arterial Alveolar Oxygen Tension Ratio (a/A)

*Note: Alternate acronym for **A** is **$pO_2(A)$**.*

*Note: Alternate acronyms for **A-a** are **$pO_2(A\text{-}a)$** and **$AaDO_2$**. Also referred to as Arterial Alveolar Oxygen Tension Difference.*

*Note: Alternate acronym for **a/A** is **$pO_2(a/A)$**.*

Entering a patient temperature is required for corresponding temperature-corrected parameters: A(T), A-a(T), a/A(T).

Note: These calculations require the sample type selection of Arterial or Capillary. If these sample types are not selected, these parameters will not be displayed.

Note: If FiO2 is not entered, these parameters will not be displayed.

These six parameters are calculated as follows.

$A = FiO_2 \times (p\text{Amb} - pH_2O) - pCO_2 \times (1/RQ - FiO_2(1/RQ - 1))$

$A(T) = FiO_2 \times (p\text{Amb} - pH_2O(T)) - pCO_2(T) \times (1/RQ - FiO_2(1/RQ - 1))$

$A\text{-}a = A - pO_2$

$A\text{-}a(T) = A(T) - pO_2(T)$

$a/A = pO_2 / A$

$a/A(T) = pO_2(T) / A(T)$

where:

RQ = Respiratory Quotient, input parameter (range 0.01-2.00). If RQ is not entered, 0.86 is used.

FiO_2 = Fraction of inspired O_2, input parameter (range 21-100, %). If FiO_2 is not entered, these parameters will not be displayed.

$pH_2O = 6.275$ kPa

$pH_2O(T) = 6.275 \times 10^{((T-37)(0.0236-0.000096(T-37)))}$ kPa, temperature units are ºC.

pAmb = ambient barometric pressure (measured by epoc Reader) kPa

T = Patient Temperature, input parameter.

Measurement Range

	Measurement Range	Reference Range
A, A(T)	5-800 mmHg	†
	0.67-106.64 kPa	†
A–a, A–a(T)	1-800 mmHg	†
	0.13-106.64 kPa	†
a/A, a/A(T)	0-100 %	†
	0-1	†

† Widely accepted reference ranges are not well established. Institutions should establish and set their own reference range values.

12.14.7 References

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   Refer to: Laboratory Professionals > Estimating and Reporting GFR > Equations and GFR Calculators>IDMS-traceable MDRD Study Equation

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