510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k113253

B. Purpose for Submission:

New device

C. Measurand:

Glucose, Sodium, Potassium and Chloride

D. Type of Test:

Quantitative, photometric and ion selective electrodes

E. Applicant:

Alfa Wassermann

F. Proprietary and Established Names:

ACE Axcel Clinical Chemistry System; ACE Ion Selective Electrode (ISE) Module; ACE Glucose Reagent

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JJE	I	862.2160 Discrete photometric chemistry analyzer for clinical use	75-Chemistry
CFR	II	862.1345, Glucose test system	75-Chemistry
JGS	II	21 CFR 862.1665 Sodium test system	75-Chemistry
CEM	II	21 CFR 862.1600 Potassium test system	75-Chemistry
CGZ	II	21 CFR 862.1170 Chloride test system	75-Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

Device Name: ACE Axcel Clinical Chemistry System, ACE Ion Selective Electrode (ISE) Module, ACE Glucose Reagent

The ACE Axcel Clinical Chemistry System is an automated, discrete, bench-top, random access analyzer that is intended for *in vitro* diagnostic use in the quantitative measurement of general chemistry assays for clinical use in physician office laboratories or clinical laboratories.
The ACE Axcel Clinical System includes an Ion Selective Electrode (ISE) module for the measurement of sodium, potassium and chloride in serum. This test is intended for use in clinical laboratories or physician office laboratories. For *in vitro* diagnostic use only.

- Sodium measurements are used in the diagnosis and treatment of diseases involving electrolyte imbalance
- Potassium measurements are used to monitor electrolyte balance and in the diagnosis and treatment of diseases conditions characterized by low or high blood potassium levels.
- Chloride measurements are used in the diagnosis and treatment of electrolyte and metabolic disorders such as cystic fibrosis and diabetic acidosis.

The ACE Glucose Reagent is intended for the quantitative determination of glucose concentration in serum using the ACE Axcel Clinical Chemistry System. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma. This test is intended for use in clinical laboratories or physician office laboratories. For *in vitro* diagnostic use only.

3. Special conditions for use statement(s):

For *in vitro* diagnostic use only. For prescription and point-of-care use.

4. Special instrument requirements:

ACE Axcel Clinical Chemistry System

I. Device Description:

The ACE Axcel Clinical Chemistry System is an automatic discrete, random access wet chemistry system intended for use in clinical laboratories or physician office laboratories that consists of a benchtop analyzer, an operation touch screen/integrated computer that prompts the user for operation input, displays data and reagent kits. The benchtop analyzer includes a single pipettor, temperature controlled reagent compartment, reaction wheel and a multi-wavelength holographic diffraction grating spectrophotometer. The ACE Axcel analyzer also includes an integrated ISE Module.

The ACE reagent kits used with the ACE Axcel Clinical Chemistry System consist of natural or brown plastic bottles containing liquid-stable reagents. The reagents have a dot code label applied to the bottom of the bottle to identify each bottle to the ACE Axcel system. Reagent kits typically have either one reagent (R1) or sometimes a second reagent (R2) and an Evap-Cap.

Glucose reagent kit contains Nicotinamide adenine dinucleotide (NAD) 2 mmol/L, Adenosine 5'-triphosphate (ATP) 4 mmol/L, Magnesium 2 mmol/L, Hexokinase (Yeast) >2000 U/L, Glucose-6-phosphate dehy7drogenase (G-6-PD) (Leuconostoc mesenteroides) >4000 U/L and buffer, stabilizers and preservatives.

The Ion-Selective Electrode (ISE) module includes a sodium electrode, a potassium electrode, a chloride electrode, a reference electrode, a cleaning solution and two calibrators (level 1 and 2). The sodium electrode membrane is a crown ether liquid-membrane. The potassium electrode membrane is a valinomycin liquid-membrane. The chloride electrode membrane is a quaternary ammonium salts polymer membrane. The ISE calibrator 1 and 2 which is included contains the following chemicals: sodium, potassium, chloride.

ISE calibrators have been previously cleared in k933862. Glucose calibrator has been previously cleared in k930104.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ACE plus ISE/Clinical Chemistry System, Alfa Wassermann

2. Predicate 510(k) number(s):
   k930104

3. Comparison to predicate

Similarities and Difference for Glucose		
Item	Candidate Device	Predicate Device
Intended Use	Intended for the quantitative determination of glucose concentrations in serum. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia and idiopathic hypoglycemia and of pancreatic islet cell carcinoma.	Same.
Calibration	Calibrated by referencing the change in absorbance of the unknown samples to the change in absorbance of the calibrator; the use of GEMCAL reference serum is recommended.	Same
Calibration Stability	30 days	Same
On-Board Stability	30days	Same
Basic Principle	Enzymatic method for glucose	Same
Analysis Temperature	37ºC	Same
Reaction Type	Endpoint	Same
Sample Type	Serum	Same
Sample Volume	3 µL	Same
Reaction Volume	318 µL	Same
Detection Limit	3.1 mg/dL	1 mg/dL
Linearity Upper Limit	757 mg/dL	750 mg/dL
Reportable Range	3-750 mg/dL	1-750 mg/dL

Similarities and Difference for Na/K/Cl		
Item	Candidate Device	Predicate Device
Intended Use	intended to measure concentrations of sodium, potassium and chloride in undiluted serum. Sodium measurements are used in the diagnosis and treatment of aldosteronism (excessive secretion of	Same

Similarities and Difference for Na/K/Cl		
	the hormone aldosterone). Diabetes insipidus (chronic excretion of large amounts of dilute urine, accompanied by extreme thirst), adrenal disease, Addison's disease (caused by destruction of the adrenal glands), dehydration, inappropriate antidiuretic hormone secretion, or other diseases involving electrolyte imbalance. Potassium measurements are used to monitor electrolyte and metabolic disorders such as cystic fibrosis and diabetic acidosis.	
Calibration	Calibration is performed automatically by the ISE module.	Same
Calibration Stability	Calibration must be performed prior to the initial run. Calibration is stable for 3 hours.	Same
Basic Principle	Ion selective electrode	Same
Analysis Temperature	Ambient	Same
Reaction Type	Electrochemical potential	Same
Sample Type	Serum	Same
Sample Volume	156 µL	Same
ISE Type	Direct (undiluted)	Same
Measuring Range	Na 40-205 mmol/L K 1.5-15 mmol/L Cl 50-200 mmol/L	Same
Expected Range	Na 136-145 mmol/L K 3.5-5.1 mmol/L Cl 98-107 mmol/L	Same

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition
CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach; Approved Guideline
CLSI EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition
CLSI EP9-A2-IR: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Second Edition
CLSI EP10-A3: Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline-Third Edition

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

Potentiometric Chemistries

The sodium, potassium and chloride are measured using ion-selective electrodes. Each electrode uses ion-specific membrane to measure the difference in ionic concentration between an inner electrolyte solution and the sample. The difference causes an electro-chemical potential to form on the membrane of the active electrode. The measured voltage difference of the sample and CAL A are used to determine the ion concentration in the sample. Two solutions contained in the ISE reagent pack CAL A and CAL B are used to perform a two-point calibration of the ion selective electrodes (ISE)

Photometric Chemistries

ACE Glucose Reagent - Glucose in serum reacts with adenosine triphosphate (ATP) in the presence of hexokinase (HK) and magnesium with the formation of glucose-6-phosphate (G-6-P) and adenosine diphosphate (ADP). Glucose-6-phosphate dehydrogenase (G-6-PD) catalyzes the oxidation of glucose-6-phosphate with NAD^+ to form 6-phosphogluconate and NADH. NADH absorbs strongly at 340 nm, whereas NAD^+ does not. The total amount of NADH formed is proportional to the initial amount of glucose present. The rate of increase in absorbance, monitored bichromatically at 340 nm/450 nm, is directly proportional to the glucose concentration in the sample.

M. Performance Characteristics (if/when applicable):

1.<u>Analytical performance:</u>

a. Precision/Reproducibility:

In-house precision

Precision studies were conducted by testing human serum pools at four levels. The samples were run 2 times per run, 2 runs per day, for a total of 22 days using one instrument (n = 80/sample). Results are summarized below.

Glucose		Sample 1	Sample 2	Sample 3	Sample 4
	Mean (mg/dL)	91.4	360.9	628	71.7
Within Run	SD	1.3	4.5	6.0	0.7
	%CV	1.4	1.2	1.0	1.0
Between Run	SD	1.2	0.0	0.0	0.3
	%CV	1.3	0.0	0.0	0.4
Between Day	SD	0.0	1.5	3.9	0.1
	%CV	0.0	0.4	0.6	0.1
Total	SD	1.7	4.7	7.1	0.7
	%CV	1.9	1.3	1.1	1.0

Sodium		Sample 1	Sample 2	Sample 3	Sample 4
	Mean (mmol/L)	95.19	143.9	170.88	137.64
Within Run	SD	0.36	1.12	1.73	0.96
	%CV	0.4	0.8	1.0	0.7
Between Run	SD	0.44	0.97	0.0	1.7
	%CV	0.5	0.7	0.0	1.2
Between Day	SD	0.51	0.61	0.57	0.0
	%CV	0.5	0.4	0.3	0.0
Total	SD	0.76	1.61	1.82	1.95
	%CV	0.8	1.1	1.1	1.4

Potassium		Sample 1	Sample 2	Sample 3	Sample 4
	Mean (mmol/L)	2.588	7.103	11.997	4.071
Within Run	SD	0.021	0.106	0.069	0.143
	%CV	0.8	1.5	0.6	3.5
Between Run	SD	0.014	0.0	0.134	0.0
	%CV	0.5	0.0	1.1	0.0
Between Day	SD	0.023	0.052	0.164	0.0
	%CV	0.9	0.7	1.4	0.0
Total	SD	0.034	0.118	0.223	0.143
	%CV	1.3	1.7	1.9	3.5

Chloride		Sample 1	Sample 2	Sample 3	Sample 4
	Mean (mmol/L)	68.26	117.52	168.65	104.47
Within Run	SD	0.49	1.04	0.84	1.02
	%CV	0.7	0.9	0.5	1.0
Between Run	SD	0.62	0.0	1.57	0.93
	%CV	0.9	0.0	0.9	0.9
Between Day	SD	0.68	0.75	1.30	0.37
	%CV	1.0	0.6	0.8	0.4

Total	SD	1.04	1.28	2.20	1.43
	%CV	1.5	1.1	1.3	1.4

Point-of-Care precision

Precision studies were also conducted at three Physician Office Laboratories (POL) with four trained operators typically found in these settings. Human serum pools at three concentrations were tested three times a day for five days on three instruments (one at each lab)(n = 15/sample). The results are presented below:

GLUCOSE			Within Run		Total	
Lab	Sample	Mean	SD	%CV	SD	%CV
POL 1	1	62.4	0.4	0.6	1.1	1.8
POL 2	1	63.3	0.7	1.1	1.0	1.6
POL 3	1	63.5	1.4	2.2	1.4	2.2
POL 1	2	299.7	1.4	0.5	1.4	0.5
POL 2	2	304.3	1.9	0.6	2.7	0.9
POL 3	2	304.0	2.5	0.8	4.0	1.3
POL 1	3	533.3	1.8	0.3	3.3	0.6
POL 2	3	540.2	3.9	0.7	3.9	0.7
POL 3	3	537.7	2.9	0.5	5.3	1.0

SODIUM			Within Run		Total	
Lab	Sample	Mean	SD	%CV	SD	%CV
POL 1	1	103.26	0.62	0.6	1.17	1.1
POL 2	1	104.07	0.78	0.7	0.87	0.8
POL 3	1	103.09	1.08	1.0	1.42	1.4
POL 1	2	137.53	1.26	0.9	1.81	1.3
POL 2	2	138.02	1.08	0.8	1.11	0.8
POL 3	2	136.78	1.03	0.8	1.62	1.2
POL 1	3	174.77	1.26	0.7	2.32	1.3
POL 2	3	175.01	1.42	0.8	1.43	0.8
POL 3	3	173	1.11	0.6	1.45	0.8

POTASSIUM			Within Run		Total	
Lab	Sample	Mean	SD	%CV	SD	%CV
POL 1	1	4.314	0.063	1.5	0.063	1.5
POL 2	1	4.310	0.067	1.6	0.067	1.6
POL 3	1	4.293	0.059	1.4	0.068	1.6
POL 1	2	7.944	0.103	1.3	0.103	1.3
POL 2	2	7.925	0.093	1.2	0.093	1.2
POL 3	2	7.954	0.109	1.4	0.109	1.4
POL 1	3	11.925	0.122	1.0	0.154	1.3
POL 2	3	11.839	0.120	1.0	0.134	1.1
POL 3	3	12.077	0.141	1.2	0.172	1.4

CHLORIDE			Within Run		Total	
Lab	Sample	Mean	SD	%CV	SD	%CV
POL 1	1	58.83	0.72	1.2	0.79	1.3
POL 2	1	58.15	0.79	1.4	1.13	1.9
POL 3	1	58.67	0.89	1.5	1.52	2.6
POL 1	2	101.53	1.13	1.1	1.13	1.1
POL 2	2	102.45	1.24	1.2	1.24	1.2
POL 3	2	103.21	1.38	1.3	1.38	1.3
POL 1	3	148.36	1.29	0.9	1.59	1.1
POL 2	3	148.73	1.61	1.1	1.61	1.1
POL 3	3	152.40	2.04	1.3	296	1.9

b. Linearity/assay reportable range:

Linearity across the assay range was confirmed by spiking serum samples to a high concentration of analyte, then diluting the sample to obtain 1-14 levels to cover the measuring range of each assay. The assigned value of the highest sample was set to its mean value. The assigned values of the other levels were calculated by multiplying the mean value by the ratios obtained from the manufacturer. Each level was tested in replicates of four. Results are summarized below:

Analyte tested	Linear regression	r^2	Samples range tested
Gluc (mg/dL)	y = 0.988x – 0.88	0.999	2 - 757
Na (mmol/L)	y = 0.991x -1.94	0.9985	40 - 205
K (mmol/L)	y = 1.001x – 0.44	0.9969	1.5 – 15
Cl (mmol/L)	y = 0.997x – 2.1	0.9987	50 – 200

Results of the study support the sponsor claims for the following measuring/linearity ranges:

Sodium	Potassium	Chloride	Glucose
40-205 mmol/L	1.5 – 15 mmol/L	50 – 200 mmol/L	3 – 750 mg/dL

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

The ISE calibrator material was previously cleared under k933862 and glucose calibrator (Gemcal) was previously cleared under k930104.

d. *Detection limit:*

The sponsor determined that the detection limit was defined by the linear range study. Please refer to the linearity study for Na, K and Cl.

In addition, the sponsor performed a detection limits study for glucose based on a modified protocol according to the CLSI EP17-A. The limit of blank was determined by assaying five low samples (serum samples) and five true blanks (human serum albumin in saline). Testing was carried out over three days on two ACE Axcel Clinical Chemistry Analyzers. Serum samples and true blanks were assayed every day for a total of 60 measurements. LoD and LoQ were determined by running 5 low samples testing 8 replicates/day for 5 days for a total of 40 measurements. The LoB was calculated to be 2.5 mg/dL and LoD was calculated to be 3.1 mg/dL. The LoQ was determined to be 3 mg/dL for glucose with an inter-assay precision of <11.6% CV.

e. *Analytical specificity:*
Interference studies were performed to determine the effects from potential interferents. The various concentration of interferent was spiked into serum pools containing glucose, sodium, potassium and chloride at normal and abnormal concentrations. All samples were tested in triplicate. Seven levels were tested for each interferent. The sponsor states that interferences are considered to be non-significant if the bias between the tested and control samples are within ±10% for all the analytes.

The tested ranges and analyte concentrations are listed in the tables below:

Glucose

Interferent	No Significant Interference at or below
Unconjugated Bilirubin	31 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides	327 mg/dL
Ascorbic Acid	6 mg/dL

Sodium

Interferent	No Significant Interference at or below
Unconjugated Bilirubin	50 mg/dL
Hemoglobin	1000 mg/dL
Lipemia (Intralipid)	689 mg/dL
Ascorbic Acid	6 mg/dL
Potassium Phosphate, Dibasic	50 mmol/L
Glucose	500 mg/dL
Calcium Chloride	216 mmol/L

Potassium

Interferent	No Significant Interference at or below
Unconjugated Bilirubin	50 mg/dL
Hemoglobin	125 mg/dL
Lipemia (Intralipid)	659 mg/dL
Ascorbic Acid	6 mg/dL
Sodium Chloride	513 mmol/L
Sodium Bicarbonate	625 mmol/L
Glucose	500 mg/dL

Chloride

Interferent	No Significant Interference at or below
Unconjugated Bilirubin	50 mg/dL
Hemoglobin	1000 mg/dL
Lipemia (Intralipid)	620 mg/dL
Ascorbic Acid	6 mg/dL
Potassium Phosphate, Dibasic	100 mmol/L
Sodium Bicarbonate	1250 mmol/L
Glucose	500 mg/dL

Based on the hemolysis interference, the sponsor has the following limitations in their labeling:

"Do not use hemolyzed samples for potassium since significant hemolysis may increase K concentration because of high levels of K in erythrocytes".

"Drugs and other substances may affect sodium, potassium, chloride, and glucose determinations. See Young, D.S.[1] for a compilation of reported interferences"

1. Young, D.S., Effects of Drugs on Clinical Laboratory Tests, 5th edition, AACC Press, Washington D.C., 2000.

f. Assay cut-off:

Not applicable.

2.Comparison studies:

a. Method comparison with predicate device:

An in-house method comparison study to the predicate device was performed with serum patient samples. A total of 122 glucose (108 native, 5 diluted and 9 spiked) serum samples, 113 Sodium (102 native, 6 diluted and 5 spiked) serum sample, 115 Potassium (103 native, 4 diluted and 8 spiked) serum samples and 111 Chloride (103 native, 3 dilutes and 5 spiked) serum samples covering the assay range were tested. The results are presented in the table below:

Test	n	Regression Equation	R^2	Standard Error	Sample range
Glucose	122	y=1.005x-0.7	0.9998	3.1	6-729 mg/dL
Sodium	113	y=1.008x-1.34	0.9963	1.65	45.1-194 mmol/L
Potassium	115	y=1.002x+0.022	0.9974	0.146	1.57-14.20 mmol/L
Chloride	111	Y=0.970x+2.28	0.9855	2.05	63.4-176 mmol/L

Additional method comparison studies were performed at three Physician Office Laboratories, with four operators. Operators assayed serum samples a total of 166 glucose (137 native, 22 spiked and 7 diluted), a total of 155 sodium (126 native, 15 spiked and 14 diluted), a total of 166 potassium (132 native, 23 spiked and 11 diluted) and a total of 155 chloride (127 native, 20 spiked and 8 diluted) samples on the Ace Axcel clinical chemistry analyzer and the ACE clinical chemistry System. The results are presented in the tables below:

Glucose

POL	n	Regression Equation	R^2	Standard Error	Sample range
1	63	y=0.980x+1.5	0.9995	5.4	24-712 mg/dL
2	56	y=1.004x+1.3	0.9992	7.0	9-693 mg/dL
3	47	y=1.014x-1.5	0.9998	3.6	20-718 mg/dL

Sodium

POL	n	Regression Equation	R^2	Standard Error	Sample range

1	57	y=1.022x-3.43	0.9994	0.91	40.4-185.4 mmol/L
2	50	y=0.999x+0.47	0.9995	0.74	56.9-185.9 mmol/L
3	48	y=1.028x-3.27	0.9917	3.07	42.5-204 mmol/L

Potassium

POL	n	Regression Equation	R^2	Standard Error	Sample range
1	62	y=1.017x-0.088	0.9978	0.182	1.99-14.73 mmol/L
2	53	y=0.968x+0.174	0.9996	0.064	1.67-14.07 mmol/L
3	51	y=1.008x-0.058	0.9973	0.167	1.56-14.77 mmol/L

Chloride

POL	n	Regression Equation	R^2	Standard Error	Sample range
1	55	y=1.019x-2.63	0.9990	0.89	59.7-195.1 mmol/L
2	52	y=0.984x+1.36	0.9996	0.55	51.5-180 mmol/L
3	48	y=1.041x-3.05	0.9885	3.05	52.4-189.6 mmol/L

b. Matrix comparison:

The device is being cleared for serum use only.

3.Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4.Clinical cut-off:

Not applicable

5.Expected values/Reference range:

Reference Values are provided in the labeling according to literature as follows:

Analyte	Serum
Glucose	70-105 mg/dL
Sodium	136-145 mEq/L
Potassium	3.5-5.1 mEq/L
Chloride	98-107 mEq/L

Tietz:N.W.Clinical Guide to Laboratory tests 3rd Ed., (WB Saunders Co. Philadelphia USA) , (1995).

Tietz:N.W.(Ed.), Fundamentals of Clinical Chemistry, (WB Saunders eds. Philadelphia USA) , (1976).

N. Instrument Name:

ACE Axcel Clinical Chemistry Analyzer

O. System Descriptions:

1.Modes of Operation:

This instrument is capable of testing several assays via self-contained reagent bottles. The instrument identifies the assay through reading a dot code label on the bottom of each reagent bottle.

2.Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes ___X_____ or No _____

3.Specimen Identification:

Barcoding or manual entry

4.Specimen Sampling and Handling:

Samples are manually placed on the instrument either by sample tube or sample cup. The system can run an individual sample or a batch of samples. Once tested the samples are removed.

5.Calibration:

On demand calibration. It is recommended to perform a calibration measurement after installing a new or fresh bottle of reagent and/or intervals that are defined for a particular test. It is recommended to recalibrate ISEs after installing a new lot of calibration solution. ISE calibration is required every 3 hours or when quality control results fall outside the established range after replacing electrode, and after ISE cleaning maintenance.

6. Quality Control:

Controls are run manually and recommended daily. Results can be stored in instrument memory for future use.

7. Room Temperature:

An ambient temperature study was conducted to show the affects on sample results when room temperature fluctuates (from 59 – 80^{o}F) . Five serum samples with analyte concentrations covering the medical decision points were tested. Calibrations were performed at each of these temperatures (59 ^{o}F, 70 ^{o}F, and 80^{o}F) and testing was performed at all the three temperatures for each calibration temperature. Room temperatures were set and maintained by thermostats in the facility. Temperatures were recorded during the study. Protocols and acceptance criteria provided are found to be adequate. Based on the ambient temperature study, the sponsor claimed that ambient temperature between 59 – 80^{o}F will not affect the performance of the device.

P. **Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:**

None

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.