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

## A. 510(k) Number:

k123322

## B. Purpose for Submission:

New reagents (Urea Nitrogen, Creatinine, Uric Acid, Creatinine Kinase) added onto ACE Alera instrument (k123018)

Addition of lithium heparin plasma samples to already cleared reagents on the ACE (k930104) and ACE Axcel (k113389) instruments.

## C. Measurand:

Urea Nitrogen (BUN), Creatinine, Uric Acid (UA), Creatine Kinase (CK)

## D. Type of Test:

Quantitative, photometric/colorimetric methods

## E. Applicant:

Alfa Wassermann Diagnostic Technologies, LLC

## F. Proprietary and Established Names:

ACE BUN/Urea Reagent
ACE Creatinine Reagent
ACE Uric Acid Reagent
ACE CK Reagent

## G. Regulatory Information:

| Product Code | Classification | Regulation | Panel |
|---|---|---|---|
| CDN | Class II | 21 CFR 862.1770<br>Urea nitrogen Test System | Clinical Chemistry (75) |
| CGX | Class II | 21 CFR 862.1225<br>Creatinine Test System | Clinical Chemistry (75) |
| KNK | Class I, reserved | 21 CFR 862.1775<br>Uric Acid Test System | Clinical Chemistry (75) |

| | | | |
|---|---|---|---|
| CGS | Class II | 21 CFR 862.1215<br>Creatine Phosphokinase/Creatine Kinase or Isoenzymes Test System | Clinical Chemistry (75) |

**H. Intended Use:**

1. Intended use(s):

2. Indication(s) for use:

The ACE BUN/Urea Reagent is intended for the quantitative determination of blood urea nitrogen (BUN) concentration in serum and lithium heparin plasma using the ACE, ACE Alera and ACE Axcel Clinical Chemistry Systems. BUN measurements are used in the diagnosis and treatment of certain renal and metabolic diseases. This test is intended for use in clinical laboratories or physician office laboratories. For *in vitro* diagnostic use only.

The ACE Creatinine Reagent is intended for the quantitative determination of creatinine concentration in serum and lithium heparin plasma using the ACE, ACE Alera and ACE Axcel Clinical Chemistry Systems. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes. This test is intended for use in clinical laboratories or physician office laboratories. For *in vitro* diagnostic use only.

The ACE Uric Acid Reagent is intended for the quantitative determination of uric acid concentration in serum and lithium heparin plasma using the ACE, ACE Alera and ACE Axcel Clinical Chemistry Systems. Uric acid measurements are used in the diagnosis and treatment of numerous renal and metabolic disorders, including renal failure, gout, leukemia, psoriasis, starvation or other wasting conditions and of patients receiving cytotoxic drugs. This test is intended for use in clinical laboratories or physician office laboratories. For *in vitro* diagnostic use only.

The ACE CK Reagent is intended for the quantitative determination of creatine kinase activity in serum and lithium heparin plasma using the ACE, ACE Alera and ACE Axcel Clinical Chemistry Systems. Measurement of creatine kinase is used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy. 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 use and use in Point-of-Care settings

4. Special instrument requirements:

   For use on the ACE, ACE Axcel and ACE Alera Clinical Chemistry Systems.

## I. Device Description:

The ACE BUN/Urea Reagent consists of a single reagent bottle containing α-Ketoglutarate (4.0 mmol/L), Urease (Jack Bean) >15,000 U/L, Glutamate dehydrogenase (GLDH) (Beef Liver) >1667 U/L, Adenosine diphosphate (ADP) (2.0 mmol/L), Nicotinamide adenine dinucleotide, reduced (NADH, 0.28 mmol/L), buffer, preservative and stabilizer.

The ACE Creatinine Reagent consists of two reagent bottles, the Sodium Hydroxide Reagent and Picric Acid Reagent. The Sodium Hydroxide Reagent (R1) contains Sodium Hydroxide (0.25 mol/L) and surfactants. The Picric Acid Reagent (R2) contains Picric Acid (20.5 mmol/L).

The ACE Uric Acid Reagent consists of a single reagent bottle containing 4-Aminoantipyrine (AAP, 0.5 mmol/L), Dichlorohydroxybenzene sulfonic acid (DHBS, 1.8 mmol/L), Peroxidase (Horseradish, > 3500 U/L), Uricase (Bacillus, > 200 U/L) and stabilizers and preservatives.

The ACE CK Reagent consists of two reagent bottles, Buffer and Substrate. The Buffer Reagent (R1) contains Imidazole Buffer (pH 6.5 at 25°C), Glucose (20 mmol/L), N- acetylcysteine (20 mmol/L), Magnesium acetate (10 mmol/L), EDTA (2 mmol/L), NADP (2 mmol/L), Hexokinase (recombinant yeast, modified, >5 KU/L). The Substrate Reagent (R2) contains Creatine phosphate (30 mmol/L), EDTA (2 mmol/L), ADP (2 mmol/L), AMP (5 mmol/L), Diadenosine pentaphosphate (10 µmol/L) and Glucose-6-phosphate dehydrogenase (E coli, >1.4 KU/L).

## J. Substantial Equivalence Information:

1. Predicate device name(s):

   ACE BUN/Urea Reagent
   ACE Creatinine Reagent
   ACE Uric Acid Reagent
   ACE CK Reagent

2. Predicate K number(s):

   k930104

3. Comparison with predicate:

1. **ACE BUN reagent:**

| Similarities and Differences | | |
|---|---|---|
| **Characteristic** | **New Device** | **Predicate Device BUN/Urea Reagent** |
| Intended Use | Same | The ACE BUN/Urea Reagent is intended for the quantitative determination of blood urea nitrogen (BUN) concentration. |
| Measurand | Same | BUN |
| Assay Method | Same | Photometric |
| Measuring Range | Same | 3 –100 mg/dL |
| Matrix | Human serum and Li heparin plasma | Human serum |

2. **ACE Creatinine Reagent:**

| Similarities and Differences | | |
|---|---|---|
| **Characteristic** | **New Device** | **Predicate Device Creatinine Reagent** |
| Intended Use | Same | The ACE Creatinine Reagent is intended for the quantitative determination of creatinine concentration. |
| Measurand | Same | Creatinine |
| Assay Method | Same | Photometric |
| Measuring Range | Same | 0.33 – 25 mg/dL |
| Matrix | Human serum and Li heparin plasma | Human serum |

**3. ACE Uric Acid reagent:**

| Similarities and Differences | | |
|---|---|---|
| **Characteristic** | **New Device**<br>**Alfa Wassermann**<br>ACE **Alera Uric Acid Reagent** | **Predicate Device**<br>**Alfa Wassermann ACE Axcel Uric Acid Reagent** |
| Intended Use | Same | The ACE Uric Acid Reagent is intended for the quantitative determination of uric acid concentration. |
| Measurand | Same | Uric Acid |
| Assay Method | Same | Photometric |
| Measuring Range | Same | 1.5 – 16 mg/dL |
| Matrix | Human serum and Li heparin plasma | Human serum |

**4. ACE CK reagent:**

| Similarities and Differences | | |
|---|---|---|
| **Characteristic** | **New Device** | **Predicate Device**<br>**CK Reagent** |
| Intended Use | Same | The ACE CK Reagent is intended for the quantitative determination of creatine kinase activity. |
| Measurand | Same | CK |
| Assay Method | Same | Photometric |
| Measuring Range | Same | 11 – 1350 U/L |
| Matrix | Human serum and Li heparin plasma | Human serum |

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

Evaluation of the Precision Performance of Quantitative Measurement Methods (CLSI EP05-A2)

Evaluation of the Linearity of Quantitative Measurement Procedures: A statistical approach (CLSI EP6-A)

Interference Testing in Clinical Chemistry (CLSI EP07-A2)

Method Comparison and Bias Estimation Using Patient Samples (CLSI EP09-A2-IR)

Protocol for Determination of Limits of Detection (CLSI EP17-A)

**L. Test Principle:**

The ACE BUN/Urea Reagent is a photometric assay in which urea in serum is hydrolyzed by urease to yield ammonia and carbon dioxide. The ammonia formed subsequently reacts with 2-oxoglutarate and NADH in the presence of glutamate dehydrogenase (GLDH) to yield glutamate and NAD. NADH absorbs strongly at 340 nm, whereas $NAD^+$ does not. The decrease in absorbance of NADH, monitored bichromatically at 340 nm/647 nm, is proportional to the urea concentration in the sample.

The ACE Creatinine Reagent is a photometric assay based on Jaffe reaction, in which serum creatinine reacts with picric acid in an alkaline medium to form a red-orange colored complex, which absorbs strongly at 505 nm. The rate of complex formation is determined by the increase of absorbance at 505 nm/573 nm during a fixed time interval; this rate is directly proportional to the creatinine concentration in the sample.

The ACE Uric Acid Reagent is based on a photometric assay in which serum uric acid is oxidized by uricase to allantoin and hydrogen peroxide, which subsequently reacts to coupled chromogen dichlorohydroxybenzene sulfonic acid (DHBS) and 4-aminoantipyrine (AAP) in a reaction catalyzed by peroxidase and produces a red colored quinoneimine complex; which are measured by the increase in absorbance at 505 nm/610 nm. This increase is directly proportional to the uric acid concentration in the sample.

The ACE CK Reagent is a coupled enzymatic reaction in which serum creatine kinase (CK) first catalyzes the conversion of creatine phosphate and adenosine diphosphate (ADP) to creatine and ATP. Subsequently, hexokinase (HK) uses the ATP produced to phosphorylate D-glucose to form D-glucose-6-phosphate and ADP. In the final reaction, the enzyme glucose-6-phosphate dehydrogenase (G-6-PDH) uses D-glucose-6-phosphate to convert nicotinamide adenine dinucleotide phosphate (NADP+) into NADPH, absorbs strongly at 340 nm. The rate of conversion of NADP+ to NADPH, which is a function of the activity of CK in the

sample, is determined by monitoring the increase in absorbance at 340 nm/378 nm.

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

1. Analytical performance:

*a. Precision/Reproducibility:*

The precision of the BUN, Creatinine, uric acid and CK assays on an in-house ACE Alera analyzer was evaluated using human serum samples at 3 concentrations of the respective measurand using 20 day precision study. The study was performed measuring each sample 2 times per run, 2 runs per day for 20 days for a total of 80 measurements per sample using 1 reagent lot. The results are provided in the table below.

| Measurand | Sample Mean (mg/dL) | Within Run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| BUN (mg/dL) | 15 | 0.3 | 2.1 | 0.5 | 3.1 |
| | 42 | 0.7 | 1.7 | 1.3 | 3.0 |
| | 74 | 1.5 | 2.0 | 2.3 | 3.2 |
| Creatinine (mg/dL) | 0.9 | 0.03 | 3.9 | 0.08 | 9.8 |
| | 1.7 | 0.04 | 2.4 | 0.12 | 7.5 |
| | 5.4 | 0.13 | 2.5 | 0.22 | 4.1 |
| UA (mg/dL) | 3.5 | 0.10 | 3.0 | 0.18 | 5.2 |
| | 6.0 | 0.14 | 2.3 | 0.25 | 4.1 |
| | 11.6 | 0.32 | 2.8 | 0.55 | 4.7 |
| CK (U/L) | 128 | 2.2 | 1.7 | 3.8 | 3.0 |
| | 378 | 6.8 | 1.8 | 11.5 | 3.0 |
| | 865 | 8.5 | 1.0 | 16.2 | 1.9 |

*Plasma and Serum in house precision study:*

The precision of the BUN, Creatinine, uric acid and CK assays for matched serum and Lithium heparin plasma samples at 3 concentrations of the respective measurand was evaluated in house over a period of 3 to 5 days. In this study, matched serum and plasma with a low concentration of measurand from a single donor was spiked to a high concentration of measurand with commercially-available analyte and then the remaining sample prepared by intermixing. CK was measured 2 times per run for 3 runs per day for 3 days (N=18). For BUN, Creatinine, and UA the study was performed measuring each sample 2 times per run, 2 runs per day for multiple days using 1 reagent lot for a total of 16 measurements per sample for BUN, 20 measurements per sample for Creatinine, 16 measurements per sample for UA. All samples were tested on the ACE, ACE Alera and ACE Axcel analyzers. The precision results are summarized in the table below.

**BUN**

| ACE analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 5 | Serum | 0.5 | 11.1 | 0.6 | 12.4 |
| 4 | Plasma | 0.4 | 10.7 | 0.5 | 12.8 |
| 46 | Serum | 0.7 | 1.4 | 0.9 | 1.8 |
| 46 | Plasma | 0.4 | 0.9 | 0.7 | 1.5 |
| 85 | Serum | 2.4 | 2.8 | 2.7 | 3.2 |
| 85 | Plasma | 2.9 | 3.4 | 3.2 | 3.8 |

| ACE Alera analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 5 | Serum | 0.4 | 7.9 | 0.6 | 13.6 |
| 4 | Plasma | 0.0 | 0.0 | 0.0 | 0.0 |
| 46 | Serum | 0.4 | 0.9 | 0.7 | 1.5 |
| 45 | Plasma | 0.5 | 1.1 | 0.9 | 1.9 |
| 85 | Serum | 1.4 | 1.6 | 1.8 | 2.1 |
| 85 | Plasma | 1.3 | 1.5 | 1.6 | 1.9 |

| ACE Axcel analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 4 | Serum | 0.4 | 8.1 | 0.5 | 12.1 |
| 4 | Plasma | 0.3 | 6.3 | 0.3 | 6.3 |
| 45 | Serum | 0.6 | 1.2 | 0.7 | 1.5 |
| 45 | Plasma | 0.6 | 1.4 | 0.6 | 1.4 |
| 85 | Serum | 1.3 | 1.5 | 1.7 | 2.0 |
| 84 | Plasma | 1.8 | 2.2 | 1.9 | 2.3 |

**CREATININE**

| ACE analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 0.68 | Serum | 0.04 | 5.8 | 0.06 | 8.5 |
| 0.65 | Plasma | 0.04 | 6.3 | 0.06 | 9.0 |
| 9.32 | Serum | 0.28 | 3.0 | 0.28 | 3.0 |
| 9.47 | Plasma | 0.23 | 2.5 | 0.25 | 2.7 |
| 18.25 | Serum | 0.13 | 0.7 | 0.35 | 1.9 |
| 18.38 | Plasma | 0.20 | 1.1 | 0.45 | 2.4 |

| ACE Alera analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 0.70 | Serum | 0.02 | 3.2 | 0.04 | 5.6 |
| 0.66 | Plasma | 0.04 | 5.5 | 0.05 | 7.8 |
| 9.24 | Serum | 0.21 | 2.3 | 0.22 | 2.4 |
| 9.41 | Plasma | 0.23 | 2.5 | 0.23 | 2.5 |
| 17.96 | Serum | 0.18 | 1.0 | 0.22 | 1.2 |
| 18.04 | Plasma | 0.19 | 1.0 | 0.22 | 1.2 |

| ACE Axcel analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 0.70 | Serum | 0.04 | 6.0 | 0.06 | 8.1 |
| 0.64 | Plasma | 0.04 | 6.6 | 0.06 | 9.3 |
| 9.31 | Serum | 0.16 | 1.7 | 0.19 | 2.1 |
| 9.42 | Plasma | 0.19 | 2.0 | 0.25 | 2.6 |
| 17.97 | Serum | 0.14 | 0.8 | 0.23 | 1.3 |
| 18.13 | Plasma | 0.31 | 1.7 | 0.43 | 2.4 |

**Uric Acid**

| ACE analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 4.5 | Serum | 0.12 | 2.6 | 0.21 | 4.5 |
| 4.3 | Plasma | 0.15 | 3.6 | 0.24 | 5.5 |
| 9.3 | Serum | 0.13 | 1.3 | 0.23 | 2.5 |
| 9.0 | Plasma | 0.06 | 0.7 | 0.17 | 1.9 |
| 15.0 | Serum | 0.26 | 1.8 | 0.31 | 2.0 |
| 14.7 | Plasma | 0.18 | 1.2 | 0.21 | 1.4 |

| ACE Alera analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 4.5 | Serum | 0.13 | 3.0 | 0.21 | 4.6 |
| 4.3 | Plasma | 0.14 | 3.3 | 0.24 | 5.5 |
| 9.2 | Serum | 0.08 | 0.8 | 0.24 | 2.6 |
| 8.9 | Plasma | 0.19 | 2.1 | 0.23 | 2.6 |
| 14.8 | Serum | 0.28 | 1.9 | 0.32 | 2.1 |
| 14.5 | Plasma | 0.26 | 1.8 | 0.28 | 1.9 |

| ACE Axcel analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (mg/dL) | Sample Type | SD | %CV | SD | %CV |
| 4.5 | Serum | 0.07 | 1.5 | 0.20 | 4.4 |
| 4.3 | Plasma | 0.12 | 2.8 | 0.19 | 4.5 |
| 9.3 | Serum | 0.08 | 0.9 | 0.26 | 2.8 |
| 9.0 | Plasma | 0.09 | 1.0 | 0.18 | 2.0 |
| 14.9 | Serum | 0.16 | 1.1 | 0.27 | 1.8 |
| 14.5 | Plasma | 0.17 | 1.2 | 0.19 | 1.3 |

**CK**

| ACE analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (U/L) | Sample Type | SD | %CV | SD | %CV |
| 79 | Serum | 3.2 | 4.0 | 3.2 | 4.0 |
| 61 | Plasma | 2.8 | 4.6 | 3.1 | 5.1 |
| 636 | Serum | 7.7 | 1.2 | 30.9 | 4.9 |
| 619 | Plasma | 11.1 | 1.8 | 25.8 | 4.2 |
| 1176 | Serum | 17.4 | 1.5 | 56.1 | 4.8 |
| 1140 | Plasma | 16.1 | 1.4 | 57.1 | 5.0 |

| ACE Alera analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (U/L) | Sample Type | SD | %CV | SD | %CV |
| 81 | Serum | 3.8 | 4.7 | 4.1 | 5.0 |
| 65 | Plasma | 1.8 | 2.8 | 2.8 | 4.4 |
| 615 | Serum | 9.4 | 1.5 | 28.6 | 4.6 |
| 605 | Plasma | 8.8 | 1.5 | 32.4 | 5.4 |
| 1125 | Serum | 7.9 | 0.7 | 55.5 | 4.9 |
| 1111 | Plasma | 14.4 | 1.3 | 51.1 | 4.6 |

| ACE Axcel analyzer | | Within Run | | Total | |
|---|---|---|---|---|---|
| Sample Mean (U/L) | Sample Type | SD | %CV | SD | %CV |
| 85 | Serum | 1.5 | 1.7 | 2.3 | 2.7 |
| 66 | Plasma | 1.8 | 2.8 | 2.1 | 3.2 |
| 682 | Serum | 3.7 | 0.5 | 31.4 | 4.6 |
| 666 | Plasma | 13.0 | 2.0 | 36.5 | 5.5 |
| 1255 | Serum | 7.2 | 0.6 | 58.4 | 4.7 |
| 1221 | Plasma | 11.7 | 1.0 | 54.7 | 4.5 |

*Serum POL precision study:*

The precision of the BUN, Creatinine, uric acid and CK assays at in-house and 3 physician office laboratories (POLs) for matched serum samples at 3 concentrations of the respective measurand was evaluated using a multiple day precision study. In this study, serum with a low concentration of measurand from a single donor was spiked to a high concentration of measurand with commercially-available analyte and then the remaining sample prepared by intermixing. The study was performed measuring each sample 2 times per run, 2 runs per day for 5 days using 1 reagent lot for a total of 20 measurements per sample on the ACE Alera analyzer. The precision results are provided in the table below.

**BUN**

| Sample Mean (mg/dL) | Site | Within Run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| 8 | In-house | 0.40 | 5.5 | 0.60 | 7.7 |
| 9 | POL-1 | 0.40 | 4.5 | 0.50 | 6.2 |
| 8 | POL-2 | 0.20 | 2.8 | 0.40 | 4.9 |
| 9 | POL-3 | 0.30 | 3.6 | 0.70 | 8.3 |
| 42 | In-house | 1.30 | 3.2 | 1.60 | 3.9 |
| 43 | POL-1 | 1.40 | 3.4 | 1.70 | 4.0 |
| 41 | POL-2 | 1.10 | 2.7 | 1.80 | 4.4 |
| 44 | POL-3 | 0.70 | 1.7 | 1.40 | 3.3 |
| 75 | In-house | 0.40 | 0.5 | 2.00 | 2.6 |
| 76 | POL-1 | 1.20 | 1.6 | 1.80 | 2.4 |
| 74 | POL-2 | 1.70 | 2.3 | 2.80 | 3.7 |
| 76 | POL-3 | 1.10 | 1.4 | 2.20 | 2.9 |

**Creatinine**

| Sample Mean (mg/dL) | Site | Within Run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| 0.58 | In-house | 0.02 | 3.2 | 0.03 | 5.3 |
| 0.53 | POL-1 | 0.03 | 6.0 | 0.05 | 9.3 |
| 0.56 | POL-2 | 0.02 | 4.2 | 0.03 | 4.4 |
| 0.55 | POL-3 | 0.02 | 4.3 | 0.04 | 6.3 |
| 8.08 | In-house | 0.11 | 1.3 | 0.28 | 3.5 |
| 7.84 | POL-1 | 0.08 | 1.1 | 0.15 | 1.9 |
| 8.21 | POL-2 | 0.14 | 1.7 | 0.23 | 2.8 |
| 7.98 | POL-3 | 0.09 | 1.1 | 0.23 | 2.9 |
| 12.65 | In-house | 0.07 | 0.5 | 0.42 | 3.3 |
| 12.32 | POL-1 | 0.10 | 0.9 | 0.42 | 3.4 |
| 12.81 | POL-2 | 0.31 | 2.4 | 0.50 | 3.9 |
| 12.27 | POL-3 | 0.12 | 1.0 | 0.44 | 3.6 |

**UA**

| Sample Mean (mg/dL) | Site | Within Run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| 2.9 | In-house | 0.10 | 3.5 | 0.13 | 4.5 |
| 3.0 | POL-1 | 0.15 | 5.2 | 0.16 | 5.3 |
| 2.9 | POL-2 | 0.09 | 3.1 | 0.10 | 3.6 |
| 3.2 | POL-3 | 0.05 | 1.6 | 0.09 | 2.9 |
| 8.0 | In-house | 0.05 | 0.7 | 0.17 | 2.1 |
| 7.6 | POL-1 | 0.13 | 1.7 | 0.21 | 2.8 |
| 7.5 | POL-2 | 0.08 | 1.0 | 0.13 | 1.8 |
| 7.9 | POL-3 | 0.07 | 0.9 | 0.25 | 3.1 |
| 12.7 | In-house | 0.18 | 1.4 | 0.22 | 1.7 |
| 11.9 | POL-1 | 0.14 | 1.2 | 0.26 | 2.2 |
| 11.6 | POL-2 | 0.27 | 2.4 | 0.27 | 2.4 |
| 12.2 | POL-3 | 0.15 | 1.2 | 0.35 | 2.9 |

**CK**

| Sample Mean (mg/dL) | Site | Within Run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| 75 | In-house | 2.50 | 3.3 | 3.30 | 4.4 |
| 73 | POL-1 | 1.40 | 1.9 | 2.60 | 3.6 |
| 70 | POL-2 | 2.20 | 3.2 | 3.50 | 5.0 |
| 70 | POL-3 | 2.10 | 3.0 | 4.10 | 5.9 |
| 516 | In-house | 8.00 | 1.5 | 8.10 | 1.6 |
| 567 | POL-1 | 10.00 | 1.8 | 14.00 | 2.5 |
| 514 | POL-2 | 6.50 | 1.3 | 8.80 | 1.7 |
| 559 | POL-3 | 6.90 | 1.2 | 14.10 | 2.5 |
| 905 | In-house | 9.50 | 1.1 | 14.00 | 1.6 |
| 995 | POL-1 | 7.60 | 0.8 | 14.40 | 1.4 |
| 899 | POL-2 | 11.40 | 1.3 | 11.60 | 1.3 |
| 977 | POL-3 | 13.00 | 1.3 | 19.60 | 2.0 |

*b. Linearity/assay reportable range:*

The sponsor assessed linearity on the ACE Alera analyzer with one run using one lot of reagents with each sample tested in triplicate. Six diluted samples with measurand concentrations evenly distributed were prepared by diluting a high measurand concentration serum pool. This yielded linearity samples with levels that spanned the measuring range of each of the four analytes (BUN, Creatinine, UA and CK) measured.

The sponsor calculated linear and polynomial regressions from mean observed values versus expected values using an unweighted regression model. The linear regressions between the expected values and the measured values are found in the table below:

| Measurand | Range tested | Slope | Intercept | $r^2$ |
|---|---|---|---|---|
| BUN (mg/dL) | 0.7-108.7 | 1.011 | 0.1 | 0.9991 |
| Creatinine (mg/dL) | 0.2-32.4 | 1.002 | 0.06 | 0.9981 |
| Uric Acid (mg/dL) | 1.1-17.3 | 0.994 | 0.1 | 0.9939 |
| CK (U/L) | 10-1416.7 | 1.053 | - 2.6 | 0.9975 |

The linearity data provided support the sponsor's claims that the reportable range of the BUN assay is 3 – 100 mg/dL, of the Creatinine assay is 0.33 – 25 mg/dL, of the Uric Acid assay is 1.5 – 16 mg/dL, and the CK assay is 11 – 1350 U/L.

Autodilution dilution study:
Sponsor performed additional auto-dilution studies to confirm the auto-dilution function (1:3) on the ACE Alera analyzer for each measurand for plasma and serum samples by comparing the autodiluted results to the manual dilution results. All samples recovered within ±10% bias.

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

Traceability:

BUN method is traceable to NIST SRM 909. Creatinine assay is traceable to NIST SRM 967. UA assay is traceable NIST SRM 909. CK assay is traceable to a commercially available human enzyme.

The BUN, Creatinine, UA and CK calibrators have been previously cleared in k930104.

d. *Detection limit:*

LoB, LoD and LoQ studies for each measurand were evaluated based upon CLSI EP-17A using the ACE Alera analyzer.

<u>LoB Test Protocol</u>

True blank samples (n = 5) were measured in replicates of 4 for 3 days for a

total of n = 60 measurements. The LoB was calculated as the mean of the 57th and 58th highest values for the true blanks.

LoD Test Protocol

Low serum-based samples (n = 5) and true blanks (n = 5) were measured in replicates of 20 per day for 3 days for a total of n = 120 measurements.

LoQ Test Protocol

LoQ was determined by evaluating 5 low level samples with multiple replicates over multiple days for a total of 40 measurements per sample. Sponsor defined LoQ as concentration with 20% CV inter-precision at the 95% confidence limit.

ACE Alera

| **Measurand** | **LoB** | **LoD** | **LoQ** |
|---|---|---|---|
| BUN (mg/dL) | 1.53 | 1.97 | 3.0 |
| Creatinine (mg/dL) | 0.14 | 0.18 | 0.33 |
| Uric Acid (mg/dL) | 1.11 | 1.34 | 1.50 |
| CK (U/L) | 4.68 | 8.30 | 11.0 |

The sponsor claimed the following measuring ranges:

| Measurand | Assay Range |
|---|---|
| BUN (mg/dL) | 3 -100 |
| Creatinine (mg/dL) | 0.33 – 25 |
| UA (mg/dL) | 1.5 – 16 |
| CK (U/L) | 11 – 1350 |

*e. Analytical specificity:*

Interference testing was performed according to CLSI EP07 to determine whether the presence of hemoglobin, triglycerides (using Intralipid as a mimic), icterus (bilirubin), and ascorbic acid may interfere with test results for each measurand using the ACE Alera analyzer.

Human serum samples were used with two different concentrations (normal and abnormal) of measurand (BUN, creatinine, UA, and CK). Each sample level was spiked with increasing amounts of interferents for a total of 7 samples with interferent. Controls samples at each level that were not spiked were used to compare with the spiked samples. The spiked and unspiked samples were tested and used to calculate % recovery (measured concentration compared to measurand concentration with zero interferent). Measurand recovery of <10% of control value was defined as non-significant interference. The results of the highest concentration tested without significant interference are summarized in the table below.

| Measurand | Icterus (mg/dL) | Hemolysis (mg/dL) | Lipemia (mg/dL) | Ascorbic Acid (mg/dL) |
|---|---|---|---|---|
| **BUN** | 70 | 500 | 2080 | 6 |
| **Creatinine** | 6.0 | 1000 | 2080 | 6 |
| **UA** | 16.9 | 125 | 893 | 1.3 |
| **CK** | 30 | 125 | 2372 | 6 |

Since hemolysis affects UA and CK results, the sponsor has the following limitations in the labeling:

> "Specimens showing any indication of hemolysis should not be analyzed. Use clear, unhemolyzed sample" For UA and CK.

Sponsor also has the following limitation for ascorbic acid in the labeling for Uric acid:

> "Ascorbic acid concentrations above 1.3 mg/dL have been shown to • interfere with this assay. Non-fasting patients taking a high dose of vitamin C may cause low uric acid levels and results should be interpreted with caution. The literature has reported that ascorbic acid has disappeared from serum samples, as an interfering substance, in less than 90 minutes."

*f. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

Method comparison studies were completed at 3 POC sites and in house following CLSI document EP9-A2. Samples were run on the ACE Clinical Chemistry System at Alfa Wassermann and the results were compared against those gathered on ACE Alera Clinical Chemistry Systems at 3 Physician Office Labs. At least 40 determinations were made in singlicate for serum samples drawn from the same individuals on each platform. To test across the assay reportable ranges, additional sets (< 6 sets) of altered samples (spiked or diluted) were used to cover the full measuring range of each analyte. Results are summarized in the table below:

| Measurand | Site | N | Range | Slope | Intercept | $r^2$ |
|---|---|---|---|---|---|---|
| BUN (mg/dL) | In-house | 53 | 3 – 88 | 1.000 (0.986–1.014) | 0.1 (-0.3–0.4) | 0.9988 |
| | POL 1 | 53 | 3 – 88 | 1.039 (1.024–1.053) | 0.3 (-0.1 – 0.6) | 0.9987 |
| | POL 2 | 53 | 3 – 88 | 1.011 (0.998–1.023) | 0.2 (-0.1–0.6) | 0.9990 |
| | POL 3 | 53 | 3 – 88 | 1.019 (0.997–1.040) | 1.0 (0.4–1.6) | 0.9972 |
| Creatinine (mg/dL) | In-house | 52 | 0.34 – 22.57 | 1.016 (1.008–1.023) | 0.0 (-0.035–0.035) | 0.9997 |
| | POL 1 | 52 | 0.34 – 22.57 | 0.987 (0.977–0.998) | -0.012 (-0.059–0.036) | 0.9993 |
| | POL 2 | 52 | 0.34 – 22.57 | 1.041 (1.031–1.051) | -0.038 (-0.085–0.010) | 0.9994 |
| | POL 3 | 52 | 0.34 – 22.57 | 1.000 (0.985–1.015) | -0.013 (-0.083–0.057) | 0.9986 |
| Uric Acid (mg/dL) | In-house | 50 | 1.7 – 14.5 | 0.992 (0.973–1.010) | 0.05 (-0.09–0.18) | 0.9978 |
| | POL 1 | 49 | 1.7 – 14.5 | 0.967 (0.936–0.998) | 0.37 0.16– 0.58) | 0.9941 |
| | POL 2 | 49 | 1.7 – 14.5 | 0.964 (0.936–0.992) | 0.21 0.02–0.40) | 0.9951 |
| | POL 3 | 49 | 1.7 – 14.5 | 0.994 (0.955–1.034) | 0.29 0.02–0.56) | 0.9941 |
| CK (U/L) | In-house | 49 | 11 – 1204 | 0.991 (0.987–0.995) | - 1.3 (-2.6–0.0) | 0.9999 |
| | POL 1 | 50 | 11 – 1204 | 1.043 (1.032–1.053) | -6.4 (-9.9–-2.8) | 0.9994 |
| | POL 2 | 49 | 11 – 1204 | 0.971 (0.962–0.980) | - 2.3 (-5.1–0.5) | 0.9995 |
| | POL 3 | 50 | 11 – 1204 | 0.983 (0.960–1.006) | - 8.7 (-16.5–-0.9) | 0.9968 |

*b. Matrix comparison:*

To characterize correlation between lithium heparin plasma and serum, a matrix comparison study was performed for each measurand using paired samples on the ACE, ACE Alera and ACE Axcel analyzers.

Data were analyzed by linear regression with 95% CI indicated in parentheses:

| Measurand | Analyzer | N | Range | Slope | Intercept | $r^2$ |
|---|---|---|---|---|---|---|
| BUN (mg/dL) | ACE | 95 | 3 – 91 | 0.979 (0.966–0.992) | 0.4 (0.0–0.7) | 0.9850 |
| | ACE Alera | 96 | 3 – 96 | 1.009 (0.995–1.023) | -0.1 (-0.5 – 0.4) | 0.9976 |
| | ACE Axcel | 51 | 3 – 100 | 1.007 (0.977–1.038) | 0.3 (-0.7–1.4) | 0.9944 |
| Creatinine (mg/dL) | ACE | 102 | 0.37 – 22.12 | 1.014 (1.000–1.029) | -0.003 (-0.068–0.062) | 0.9974 |
| | ACE Alera | 102 | 0.41 – 23.15 | 1.050 (1.038–1.062) | -0.077 (-0.124– -0.029) | 0.9984 |
| | ACE Axcel | 56 | 0.37 – 23.45 | 1.003 (0.993–1.013) | 0.009 (-0.054–0.071) | 0.9993 |
| Uric Acid (mg/dL) | ACE | 97 | 2.5 – 14.0 | 1.008 (0.980–1.036) | -0.14 (-0.34–0.06) | 0.9906 |
| | ACE Alera | 95 | 2.5 – 14.4 | 1.028 (0.989–1.066) | -0.29 (-0.57– - 0.01) | 0.9836 |
| | ACE Axcel | 55 | 1.8 – 15.6 | 1.025 (0.981–1.069) | -0.09 (-0.39–0.21) | 0.9836 |
| CK (U/L) | ACE | 97 | 11 – 1234 | 0.997 (0.980–1.014) | - 0.6 (-6.1–4.9) | 0.9965 |
| | ACE Alera | 96 | 14 – 1211 | 0.978 (0.960–0.996) | 0.1 (-5.2–5.5) | 0.9960 |
| | ACE Axcel | 55 | 17 – 1315 | 1.006 (0.993–1.019) | - 0.5 (-4.74–3.74) | 0.9990 |

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:

Expected values are based on the literature reference:

[1]Tietz, N.W. (Ed.), Clinical Guide to laboratory Tests, 3rd edition, W.B.Saunders, Philadelphia, PA (1995); [2]Wu, A.H.B. (Ed.), Tietz Clinical Guide to Laboratory Tests, 4th edition, Saunders, Elsevier, St. Louis, MO (2006).

[1]BUN: 6 – 20 mg/dL

[1]Creatinine: Male: 0.9 – 1.3 mg/dL, Female: 0.6 – 1.1 mg/dL

[2]UA: Male: 3.5 – 7.2 ng/dL, Female: 2.6 – 6.0 mg/dL

[1]CK: Male: 38 – 174 U/L, Female: 26 – 140 U/L

**N. Proposed Labeling:**

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

**O. Conclusion:**

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