510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K210452

B Applicant

Abbott Ireland Diagnostics Division

C Proprietary and Established Names

Creatinine2

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CGX	Class II	21 CFR 862.1225 - Creatinine Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Creatinine

C Type of Test:

Quantitative, photometric/colorimetric

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Creatinine2 assay is used for the quantitation of creatinine in human serum, plasma, or urine on the ARCHITECT c System.
The Creatinine2 assay is to be used as an aid in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

ARCHITECT c8000 System

IV Device/System Characteristics:

A Device Description:

The Creatinine2 assay is comprised of a reagent kit that is run on the ARCHITECT c8000 System. Each kit has two reagents; R1 and R2. R1 contains sodium hydroxide (0.8 mol/L) and R2 contains picric acid (5.500 g/L). The Creatinine2 assay is calibrated using the Consolidated Chemistry Calibrator, which is required but not provided with the kit. The product labeling recommends running controls containing creatinine, but these are not provided with the kit.

B Principle of Operation:

The methodology of the Creatinine2 assay is that of a colorimetric assay. At alkaline pH, by addition of sodium hydroxide, creatinine in the sample chemically reacts with a picric acid reagent to form a creatinine-picrate complex. This reaction product has an absorbance at 500 nm. The rate of increase in absorbance is directly proportional to the concentration of creatinine in the sample.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Creatinine

B Predicate 510(k) Number(s):
k083809

C Comparison with Predicate(s):

Device & Predicate Device(s):	k210452	k083809
Device Trade Name	Creatinine2	Creatinine
General Device Characteristic Similarities		
Intended Use/Indications For Use	The assay is used for the quantitation of creatinine.	Same
Method	Kinetic alkaline picrate	Same
Traceability	NIST SRM 967 for serum/plasma and NIST SRM 914 for urine.	Same
General Device Characteristic Differences		
Specimen types	Serum, K2EDTA plasma, lithium heparin plasma, sodium heparin plasma, and urine	Serum, lithium heparin plasma, sodium heparin plasma, and urine

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition.

CLSI EP07-A3 Interference Testing in Clinical Chemistry; Approved Guideline —Third Edition.

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   The sponsor provided separate precision studies supporting use of: (1) serum and (2) urine.

   Serum
   In the study, five serum based controls were internally prepared and also obtained from a commercial source. Each of the five samples was tested on three ARCHITECT c8000 instruments using three lots of creatinine reagent kits in duplicates per run, two runs per day, over 20 day for a total of 80 measurements per instrument/lot. The results for each sample per instrument/lot, presented in the table below were analyzed for variance by an ANOVA method for the factors of within-run, between-run, and between-day. The within-laboratory

SD and %CV were estimated using the summation of the within-run, between-run, and between-day variance components.

Instrument 1/reagent lot 1

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	1.37	0.015	1.1	0.008	0.6	0.011	0.8	0.020	1.5
Control 2	5.78	0.054	0.9	0.000	0.0	0.034	0.6	0.064	1.1
Control 3	0.26	0.008	3.2	0.007	2.6	0.000	0.0	0.011	4.1
Control 4	25.47	0.137	0.5	0.076	0.3	0.143	0.6	0.212	0.8
Control 5	35.64	0.203	0.6	0.050	0.1	0.155	0.4	0.260	0.7

Instrument 2/reagent lot 2

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	1.42	0.015	1.0	0.013	0.9	0.046	3.3	0.050	3.5
Control 2	5.91	0.035	0.6	0.037	0.6	0.138	2.3	0.147	2.5
Control 3	0.25	0.008	3.1	0.007	2.6	0.005	1.9	0.011	4.5
Control 4	26.00	0.121	0.5	0.203	0.8	0.538	2.1	0.588	2.3
Control 5	36.36	0.130	0.4	0.182	0.5	0.744	2.0	0.777	2.1

Instrument 3/reagent lot 3

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	1.41	0.013	0.9	0.005	0.4	0.007	0.5	0.016	1.1
Control 2	5.75	0.031	0.5	0.010	0.2	0.034	0.6	0.047	0.8
Control 3	0.25	0.009	3.5	0.002	0.6	0.004	1.5	0.010	3.9
Control 4	25.24	0.087	0.3	0.032	0.1	0.160	0.6	0.185	0.7
Control 5	35.27	0.146	0.4	0.000	0.0	0.243	0.7	0.283	0.8

Urine

In the study, five human urine based controls were internally prepared and also obtained from a commercial source prepared. Each of the five samples was tested on three ARCHITECT c8000 instruments using three lots of creatinine reagent kits in duplicates per run, two runs per day, over 20 day for a total of 80 measurements per instrument/lot. The results for each sample per instrument/lot, presented in the table below were analyzed for variance by an ANOVA method for the factors of within-run, between-run, and between-day. The within-laboratory SD and %CV were estimated using the summation of the within-run, between-run, and between-day variance components.

Instrument 1/reagent lot 1

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	56.93	0.516	0.9	0.000	0.0	0.887	1.6	1.027	1.8
Control 2	129.69	1.309	1.0	0.000	0.0	1.885	1.5	2.295	1.8
Control 3	5.29	0.185	3.5	0.028	0.5	0.118	2.2	0.221	4.2
Control 4	273.71	1.700	0.6	0.593	0.2	1.974	0.7	2.671	1.0
Control 5	690.32	5.197	0.8	0.000	0.0	5.588	0.8	7.631	1.1

Instrument 2/reagent lot 2

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	57.77	0.491	0.9	0.224	0.4	1.065	1.8	1.194	2.1
Control 2	132.61	1.165	0.9	0.000	0.0	2.935	2.2	3.158	2.4
Control 3	5.37	0.233	4.3	0.081	1.5	0.160	3.0	0.294	5.5
Control 4	278.12	1.958	0.7	1.276	0.5	4.424	1.6	5.003	1.8
Control 5	701.12	3.303	0.5	2.664	0.4	12.123	1.7	12.844	1.8

Instrument 3/reagent lot 3

		Within-Run		Between-Run		Between-Day		Within-Laboratory	
Sample	Mean (mg/dL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	56.29	0.526	0.9	0.000	0.0	0.577	1.0	0.781	1.4
Control 2	128.92	0.772	0.6	0.572	0.4	1.593	1.2	1.860	1.4
Control 3	5.25	0.246	4.7	0.077	1.5	0.000	0.0	0.258	4.9
Control 4	269.85	1.539	0.6	0.000	0.0	3.396	1.3	3.728	1.4
Control 5	678.57	3.928	0.6	1.835	0.3	8.666	1.3	9.690	1.4

2. Linearity:

Linearity of the Creatinine2 assay on the ARCHITECT c8000 across the analytical measurement range was established in two studies measuring samples at concentrations spanning the measurement range using one instrument and one reagent kit lot. In each study, a high level creatinine samples was inter-mixed with a low level creatinine samples with known dilutions to prepare samples which were uniformly distributed across the measurement range. At least one concentration was included which exceeded the claimed measurement range.

Serum:

Each of the 13 samples were measured in replicates of four on the ARCHITECT c8000 system. The observed creatinine concentrations versus the expected concentrations were assessed for a linear response. Based on the results, the sponsor concluded that the creatinine

test system demonstrated a linearity over the claimed range of 0.09 to 37.34 mg/dL. The linear regression summary is given below.

Range tested	Slope	Intercept	R^2
0.08 to 40.0 mg/dL	0.999	-0.01	0.9999

Urine:
Each of the 12 samples were measured in replicates of four. The observed creatinine concentrations versus the expected concentrations were assessed for a linear response . Based on the results, the sponsor concluded that the creatinine test system demonstrate linearity over the claimed range of 2.54 to 740 mg/dL. The linear regression summary is given below.

Range tested	Slope	Intercept	R^2
1.24 to 871 mg/dL	1.0049	-0.11	1.0000

3. Analytical Specificity/Interference:
The analytical specificity of the creatinine assay on the ARCHITECT c8000 was established by conducting interference testing following the recommendations in CLSI EP07 ED3.

Serum
Interference from exogenous and endogenous substances was assessed using serum spiked with creatinine at two concentrations of 0.6 mg/dL and 2.0 mg/dL. Each spiked sample was further divided into two aliquots: test (with added interferent) and control (with no added interferent, except total protein with normal level of 7 g/dL). Each sample was tested in 10 replicates using one lot and one instrument. A substance was identified as an interferent if the difference in the mean between the control and test sample was outside of ±10% at the target levels.

The following table lists the highest concentration of each substance at which no significant interference was found. For any substances identified as an interferent, dose response testing and analysis was conducted to assess the highest concentration limit below which no significant interference is expected.

Substance	Highest concentration tested at which no interference was observed
Endogenous	
Acetoacetate	20 mg/dL
Conjugated Bilirubin	20 mg/dL
Unconjugated Bilirubin	8 mg/dL
Glucose	250 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides	750 mg/dL
Exogenous	
Acetaminophen	160 mg/dL
Acetohexamide	0.5 mg/dL
Acetylcysteine	150 mg/dL

Substance	Highest concentration tested at which no interference was observed
Acetylsalicylic acid	30 mg/dL
Ampicillin-Na	80 mg/dL
Ascorbic acid	60 mg/dL
Azlocillin	0.7 g/dL
Biotin	3510 ng/mL
Ca-dobesilate	60 mg/dL
Cefotaxime	53 mg/dL
Cefoxitin	4.7 mg/dL
Cephalothin	2 mg/dL
Cyclosporine	2 mg/dL
Doxycycline	20 mg/dL
Eltrombopag	1 mg/dL
Hydroxocobalamin (Cyanokit)	18.7 mg/dL
Ibuprofen	220 mg/dL
Levodopa	8 mg/dL
Methyldopa	10 mg/dL
Metronidazole	130 mg/dL
Nitrofurantoin	0.3 mg/dL
Nitroglycerin	0.015 mg/dL
Norfenefrine	4 mg/dL
Phenylbutazone	330 mg/dL
Rifampicin	50 mg/dL
Sodium Heparin	4 U/mL
Sulbactam	240 mg/dL
Sulfamethoxazole	40 mg/dL
Sulfapyridine	30 mg/dL
Sulfasalazine	500 mg/dL
Theophylline	60 mg/dL
Trimethoprim	5 mg/dL

Substance	Effect on test results when interferent is above the concentration limit in the table above
Conjugated Bilirubin	Decreased creatinine results
Unconjugated Bilirubin	Decreased creatinine results
Glucose	Increased creatinine results
Triglycerides	Increased creatinine results
Acetohexamide	Increased creatinine results
Azlocillin	Increased creatinine results
Cefoxitin	Increased creatinine results
Cephalothin	Increased creatinine results
Eltrombopag	Decreased creatinine results
Hydroxocobalamin (Cyanokit)	Increased creatinine results
Methyldopa	Decreased creatinine results

Total Protein
Interference from total protein was assessed using serum spiked with creatinine at concentrations of 0.6, 1.5, and 2.0 mg/dL. The sponsor defined interference as > ±10% difference between the mean of the control and test sample.

Creatinine conc.	Concentration lower limit with no significant interference	Concentration upper limit with no significant interference	Effect on test results when concentration below the lower limit	Effect on test results when concentration above the upper limit
0.6 mg/dL[1]	5.4 g/dL	8.4 g/dL	Decreased creatinine results	Increased creatinine results
1.5 mg/dL[1]	5.1 g/dL	10 g/dL	Decreased creatinine results	Increased creatinine results
2.0 mg/dL[2]	-	11 g/dL	Decreased creatinine results	Increased creatinine results

[1]Test results compared to a control sample with total protein concentration of 7.0 g/dL.
[2]Test results compared to a control sample with total protein concentration of 5.7 g/dL.

The sponsor includes the following limitations in the product labeling:

> The Creatinine2 assay is susceptible to interference from cephalosporin class antibiotics and eltrombopag at therapeutically relevant interferent concentrations. The assay is also susceptible to interference from acetohexamide, bilirubin (conjugated and unconjugated), glucose, hydroxocobalamin, and total protein.

Urine
Interference from exogenous and endogenous substances was assessed using a normal urine pool that was supplemented with a creatinine stock solution to yield a high creatinine sample with a target concentration of 400 mg/dL. A low creatinine sample was prepared by diluting a normal urine pool with artificial urine to yield a sample with a target concentration of 15 mg/dL. Each low and high sample was further divided into two aliquots: control (with no added interferent) and test (with added interferent). Each sample was tested in 10 replicates using one lot and one instrument. A substance was identified as an interferent if the difference in the mean between the control and test sample was outside of ± 10% at target levels of 15 mg/dL and 400 mg/dL.

The following table lists the concentrations of each substance at which no significant interference was found. For any substances identified as an interferent, dose response testing and analysis was conducted to assess the highest concentration limit below which no significant interference is expected.

Substance	Highest concentration tested at which no significant interference was observed
Endogenous and urine additives	
Acetic Acid	6.25 mL/dL

Substance	Highest concentration tested at which no significant interference was observed
Acetoacetate	480 mg/dL
Ascorbate	220 mg/dL
Boric Acid	250 mg/dL
Glucose	1000 mg/dL
Hydrochloric Acid (6N)	2.5 mL/dL
Nitric Acid	5.0 mL/dL
Protein	50 mg/dL
Sodium Carbonate	1.25 g/dL
Sodium Fluoride	400 mg/dL
Sodium Oxalate	60 mg/dL
Urobilinogen	40 mg/dL
Exogenous	
Acetaminophen	16 mg/dL
Acetylcysteine	15 mg/dL
Biotin	4250 ng/mL
Cefoxitin	100 mg/dL
Cephalothin	180 mg/dL
Homogentisic acid	350 mg/dL
Hydroxocobalamin (Cyanokit)	18 mg/dL
Ibuprofen	22 mg/dL
Levodopa	70 mg/dL
Methyldopa	2 mg/dL
Nitrofurantoin	15 mg/dL
Nitrofurazone	0.3 mg/dL

Substance	Effect on test results when interferent is above the concentration limit in the table above
Cefoxitin	Increased creatinine results
Levodopa	Increased creatinine results

4. Assay Reportable Range:

   See section A.2 Linearity

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Traceability
   The Creatinine2 assay is traceable to the NIST SRM 967a (serum/plasma) or NIST SRM 914a (urine).

6. Detection Limit:
   Detection capability studies of the creatinine assay on the ARCHITECT c8000 with serum and urine for limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) was conducted following the recommendations in CLSI EP17-A2.

Serum

LoB
The LoB for the creatinine assay was evaluated using a zero-analyte sample. The sample was measured in 60 replicates using each of three lots of the Creatinine2 reagent kits and two instruments (total of six instrument and reagent lot combinations). The LoB was analyzed as the 95th percentile from n = 60 replicates.

LoD
The LoD was evaluated using eight low-level samples. The samples were tested in replicates of 10 using each of three lots of the Creatinine2 reagent kits and two instruments.
The LoD was analyzed using a parametric data analysis where the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

LoQ
To determine the LoQ, samples near the lower limit of the assay were run in replicates of 10 using each of three lots of the Creatinine2 reagent kits and two instruments. The LoQ was defined as the lowest concentration of analyte which has imprecision less than or equal to 20% CV.

Urine

LoB
The LoB for the creatinine assay was evaluated using a zero-analyte sample. The sample was measured in 60 replicates using each of three lots of the Creatinine2 reagent kits and two instruments (total of six instrument and reagent lot combinations). The LoB was analyzed as the 95th percentile from n = 60 replicates.

LoD
The LoD was evaluated using eight low-level samples. The samples were tested in replicates of 10 using each of three lots of the Creatinine2 reagent kits and two instruments. The LoD was analyzed using a parametric data analysis where the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

LoQ
To determine the LOQ, samples near the lower limit of the assay were run in replicates of 10 using each of three lots of the Creatinine2 reagent kits and two instruments. The LoQ was defined as the lowest concentration of analyte which has imprecision less than or equal to 20% CV.

The results from all studies, using the maximum value found across all lots and instruments are summarized in the table below.

	LoB	LoD	LoQ
serum	0.02	0.04	0.09 mg/dL
urine	0.70	1.05	2.30 mg/dL

7. Assay Cut-Off:
   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   The accuracy of the creatinine assay on the ARCHITECT c8000 for serum and urine was evaluated for agreement with the predicate device by an internal method comparison study.

   Serum
   In the study, a total of 128 serum samples were tested using three lots of the creatinine reagent kit, and one lot each of calibrator and controls across two instruments. 3.9% (5/128) of samples were prepared by spiking or diluting specimens. The data were analyzed by Passing-Bablok regression analysis comparing the first replicate of the candidate device result to the average of duplicates result of the comparator device:

N	Concentration range, comparator device (mg/dL)	Regression Equation	r
128	0.47 – 35.7	y = 0.96x - 0.01	1.00

   Urine
   A total of 129 urine samples were tested using three lots of the creatinine reagent kit, and one lot each of calibrator and controls across two instruments. Less than 10% (7.0% [9/129]) of samples were prepared by spiking or diluting specimens. The data were analyzed by Passing-Bablok regression analysis comparing the first replicate of the candidate device result to the average of duplicates result of the comparator device:

N	Concentration range, comparator device (mg/dL)	Regression Equation	r
129	6.6 – 727.6	y = 1.01x – 1.23	1.00

2. Matrix Comparison:
   A matrix equivalency study was conducted to support use of the Creatinine2 assay with additional specimen matrix types claimed in the product labeling: K2EDTA plasma, lithium heparin plasma, lithium heparin (separator tube) plasma, serum (separator tube), and sodium heparin plasma. In the study, donor matched venous specimens were collected into tubes of each aforementioned anticoagulant. Each specimen was tested in singlicate using one lot of kit and one ARCHITECT c8000 instrument, and the result compared to the mean of triplicate serum measurements. A total of 11.3% (9/80) of the blood samples in the collection tubes were supplemented with creatinine stock solution to create samples that spanned the analytical measuring interval of the assay. A Passing-Bablok evaluation was performed, regressing the concentration from the first replicate of each donor's evaluation tube (y-axis) versus the mean concentration of the control tube (x-axis). The slope and intercept of the regression line, and the two-sided 95% CI around the slope and intercept were calculated. The results are summarized as follows, and support the claimed use of K2EDTA plasma,

lithium heparin plasma, lithium heparin (separator tube) plasma, serum (separator tube), and sodium heparin plasma with the Creatinine2 assay:

Collection Tube	N	Min	Max	r	Intercept (95% CI)	Slope (95% CI)
Dipotassium EDTA	80	0.38	21.46	1.00	0.02 (0.00, 0.03)	0.98 (0.97, 1.00)
Lithium heparin	80	0.39	23.24	1.00	0.01 (0.00, 0.03)	0.98 (0.97, 1.00)
Sodium heparin	80	0.40	20.75	1.00	0.02 (-0.01, 0.04)	0.97 (0.95, 1.00)
Lithium heparin (separator tube)	80	0.39	26.46	1.00	0.01 (0.00, 0.03)	0.99 (0.97, 1.00)
Serum (separator tube)	80	0.39	22.02	1.00	0.01 (0.00, 0.02)	0.99 (0.98, 1.00)

C Clinical Studies:

1. Clinical Sensitivity:
   Not applicable.

2. Clinical Specificity:
   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):
   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The expected values for creatinine in adults with serum and urine are from literature references.

Serum, adults

Age	Range, mg/dL
18 years - < 41 years Female	0.5 - 1.0
18 years - < 41 years Male	0.6 - 1.2
41 years - < 61 years Female	0.5 - 1.1
41 years - < 61 years Male	0.6 - 1.3
61 years and above Female	0.5 - 1.2
61 years and above Male	0.7 - 1.3

Source: Pagana K, Pagana T. Mosby's Manual of Diagnostic and Laboratory Tests. 5th ed. Mosby; 2014.

Urine, random, adults

Age	Range, mg/dL
Male < 40 years	24 - 392
Male ≥ 40 years	22 - 328
Female < 40 years	16 - 327
Female ≥ 40 years	15 - 278

Source: Wu AHB, editor. Tietz Clinical Guide to Laboratory Tests. 4th ed. St. Louis, MO: Elsevier Saunders; 2006.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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