



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

I Background Information:

A 510(k) Number

K242685

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

Atellica® CH Creatinine_3 (Crea3)

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 method

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Atellica® CH Creatinine_3 (Crea3) assay is for in vitro diagnostic use in the quantitative determination of creatinine in human serum, plasma (lithium heparin, dipotassium EDTA, and sodium heparin), and urine using the Atellica® CH Analyzer. Such measurements are used in the diagnosis and treatment of renal diseases, and in monitoring renal dialysis.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Atellica® CH Analyzer

IV Device/System Characteristics:**A Device Description:**

The Atellica® CH Creatinine_3 (Crea3) assay kit has 2 major reagent packs. Reagent pack 1 (P1) contains 21.8 mL of sodium hydroxide (1.0 mol/L), and reagent pack 2 (P) contains 13.26 mL of lithium picrate (25 mmol/L).

The Atellica® CH Creatinine_3 (Crea3) assay is for in vitro diagnostic use with the Atellica® CH Analyzer (previously cleared under K151767).

B Principle of Operation:

The Atellica® CH Crea3 assay is based on the reaction of picrate with creatinine in an alkaline medium. The technique is based on modified kinetic Jaffe technique with rate blanking and intercept correction. In the presence of a strong base such as sodium hydroxide, picrate reacts with creatinine to form a red chromophore creatinine picrate complex. The rate of complex formation is measured at 505/571 nm and is proportional to the creatinine concentration in the sample. Rate blanking is used to reduce interference from non-specific serum/plasma protein interactions with the reagent.

V Substantial Equivalence Information:**A Predicate Device Name(s):**

Atellica® CH Creatinine_2 (Crea_2)

B Predicate 510(k) Number(s):

K161494

C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>K242685</u>	<u>K161494</u>
Device Trade Name	Atellica® CH Creatinine_3 (Crea3)	Atellica® CH Creatinine_2 (Crea_2)
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Atellica® CH Creatinine_3 (Crea3) assay is for in vitro diagnostic use in the quantitative determination of creatinine in human serum, plasma, and urine using the Atellica® CH Analyzer. Measurements are used in the diagnosis and treatment of renal diseases, and in monitoring renal dialysis.	Same
Device Technology	Modified Jaffe methodology (creatinine alkaline picrate) with photometric detection.	Same
Assay Range / Measuring Interval	Serum: 0.15 mg/dL to 30.00 mg/dL Urine: 3.00 mg/dL to 245.00 mg/dL	Same
Standardization	NIST SRM967	Same
General Device Characteristic Differences		
Sample Type	Serum, lithium heparin plasma, dipotassium EDTA plasma, sodium heparin plasma, urine	Serum, Plasma (Lithium Heparin), urine

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures, Third Edition.

CLSI EP06-Ed2: Evaluation of the Linearity of Quantitative Measurement Procedures, Second Edition.

CLSI EP07-Ed3: Interference Testing in Clinical Chemistry, 3rd Edition.

CLSI EP09C-Ed3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples, 3rd Edition.

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

CLSI EP25-Ed2: Evaluation of Stability of In Vitro Diagnostic Medical Laboratory Test Reagents, Second Edition.

CLSI EP28-A3C: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Third Edition.

CLSI EP32-R: Metrological Traceability and its Implementation

CLSI EP37-Ed1: Supplemental Tables for Interference Testing in Clinical Chemistry

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision was determined in accordance with CLSI EP05-A3. Samples were assayed on the Atellica® CH Analyzer in duplicate in 2 runs per day for 20 days for a total of 80 replicates. The results are summarized in the table below:

Specimen Type	Mean mg/dL	Repeatability		Within-Lab	
		SD mg/dL	CV (%)	SD mg/dL	CV (%)
Serum 1	0.38	0.006	1.6	0.012	3.2
Serum 2	0.73	0.023	3.2	0.029	4.0
Serum 3	0.73	0.006	0.8	0.019	2.6
Serum 4	1.18	0.007	0.6	0.019	1.6
Serum QC 1	1.85	0.007	0.4	0.024	1.3
Serum QC 2	6.21	0.011	0.2	0.067	1.1
Serum 5	17.39	0.035	0.2	0.189	1.1
Serum 6	28.54	0.056	0.2	0.317	1.1
Urine 1	56.74	0.102	0.2	0.746	1.3
Urine 2	135.80	0.206	0.2	1.601	1.2
Urine QC 1	195.79	0.253	0.1	2.376	1.2

Reproducibility was determined in accordance with CLSI EP05-A3. Samples were assayed on the Atellica® CH Analyzer with n=5 in 1 run for 5 days using 3 instruments and 3 reagent lots at three sites (one instrument and three lots of reagents per site) for a total of 225 replicates per sample. The data were analyzed to calculate the following components of

precision: repeatability, between-day, between-lot, between-instrument, and reproducibility (total). The results are summarized as below:

Sample	Mean mg/dL	Repeatability		Between-Day		Between-Lot		Between-Instrument		Reproducibility	
		SD mg/dL	CV %	SD mg/dL	CV %	SD mg/dL	CV %	SD mg/dL	CV %	SD mg/dL	CV %
Serum 1	0.40	0.014	3.5	0.007	1.8	0.011	2.8	0.006	1.5	0.020	5.0
Serum 2	0.72	0.015	2.1	0.021	2.9	0.007	1.0	0.014	1.9	0.030	4.2
Serum 3	1.21	0.009	0.7	0.015	1.2	0.013	1.1	0.013	1.1	0.025	2.1
Serum QC 1	1.90	0.011	0.6	0.021	1.1	0.006	0.3	0.014	0.7	0.028	1.5
Serum QC 2	6.31	0.030	0.5	0.052	0.8	0.023	0.4	0.040	0.6	0.076	1.2
Serum 4	17.62	0.048	0.3	0.113	0.6	0.000	0.0	0.090	0.5	0.152	0.9
Serum 5	28.76	0.105	0.4	0.192	0.7	0.079	0.3	0.153	0.5	0.278	1.0
Urine 1	57.23	0.213	0.4	0.475	0.8	0.177	0.3	0.681	1.2	0.875	1.5
Urine 2	137.89	0.511	0.4	0.842	0.6	0.385	0.3	1.577	1.1	1.898	1.4
Urine QC 1	199.45	0.913	0.5	1.659	0.8	0.655	0.3	2.398	1.2	3.125	1.6

2. Linearity:

A linearity study was performed in accordance with CLSI EP06-Ed2. Samples were prepared by mixing high and low concentration samples to span the measurement interval; at least 9 samples were used to evaluate the entire measuring interval for serum and urine. Five replicates were tested for each sample and the mean of these replicates was used for the calculation. The concentrations for serum samples ranged from 0.12 - 38 mg/dL and the concentrations for urine samples ranged from 1.33 - 264 mg/dL. The results showed that the deviation from linearity did not exceed 5% for samples within the measuring range.

The regression statistics of the serum linearity study:

$$Y=1.040x+0.053, r: 0.999$$

The regression statistics of the urine linearity study:

$$Y=1.002x+0.160, r = 1.000$$

The results of the linearity studies support the claimed analytical measuring range from 0.15 mg/dL to 30.00 mg/dL for serum/plasma, and 3.00 mg/dL to 245.00 mg/dL for urine for the candidate device.

3. Analytical Specificity/Interference:

The evaluation of potential interferents followed the recommendations in CLSI EP07-Ed3.

Serum

Human serum pools were split into control and test pools. The test pools were spiked with the interferences, and the control pools were spiked with an equivalent volume of compound the interference was prepared in. For serum samples, low-level analyte pool was native serum (creatinine concentration of 0.60 mg/dL), and the high-level analyte pool was native serum spiked with creatinine (creatinine concentration of 2.0 mg/dL). Five replicates were tested per sample. Substances identified with > 10% (at an analyte concentration of 2.00 mg/dL) or ± 0.15 mg/dL (at an analyte concentration of 0.60 mg/dL) bias were considered to have interfered. For any substances identified as an interference, dose response testing and analysis was conducted to assess the highest concentration limit below which no significant interference was observed.

Hemolysis, Icterus, and Lipemia (HIL) results are summarized as below:

Substance	Highest concentration tested that showed no interference (mg/dL)
Hemoglobin	1000
Conjugated Bilirubin	40
Unconjugated Bilirubin	45
Lipemia (from Intralipid®)	2250
Lipemia (from Triglyceride Fraction)	3000

The table below lists the highest concentrations of each substance at which no significant interference was found in Serum.

Substance	Highest concentration tested that showed no interference
Acetylcysteine (N-Acetylcysteine)	150 mg/L
Acetylsalicylic Acid	30 mg/L
Cefoxitin	23.5 mg/L
Glucose	250 mg/dL
Ibuprofen	220 mg/L
Total Protein	10 g/dL
Acetaminophen	160 mg/L
Acetoacetate	20 mg/dL
Acetohexamide	1.0 mg/dL
Ampicillin-Na	80 mg/L
Ascorbic Acid	60 mg/L
Azlocillin	7 g/L
Biotin	4250 ng/mL
Ca-Dobesilate	60 mg/L
Cefotaxime	53 mg/dL
Cephalothin	11 mg/dL
Cyclosporine	2 mg/L
Doxycycline	20 mg/L

Substance	Highest concentration tested that showed no interference
Eltrombopag	300 mg/L
Hydroxocobalamin (Cyanokit)	250 mg/L
Levodopa	8 mg/L
Methyldopa	100 mg/L
Metronidazole	130 mg/L
Nitrofurantoin	0.3 mg/dL
Nitroglycerin	0.015 mg/L
Norefefrine	4 mg/L
Phenylbutazone	330 mg/L
Rifampicin	50 mg/L
Sodium Heparin	4 U/mL
Sulbactam	240 mg/L
Sulfamethoxazole	40 mg/dL
Sulfapyridine	30 mg/dL
Sulfasalazine	500 mg/L
Theophylline (1.3-dimethylxanthine)	60 mg/L
Trimethoprim	5 mg/dL

Interference beyond $\pm 10\%$ or ± 0.15 mg/dL for Serum

Substance	Substance Concentration	Analyte concentration (mg/dL)	Bias
Acetohexamide	2.0 mg/dL	0.59	0.22 mg/dL
	2.0 mg/dL	2.11	10.4%
Cefoxitin	1650 mg/L	0.58	5.37 mg/dL
	1650 mg/L	2.11	243.6%
	6600 mg/L	0.58	20.85 mg/dL
	6600 mg/L	2.11	947.9%
Cephalothin	45 mg/dL	0.60	0.20 mg/dL
	45 mg/dL	2.07	11.1%
	180 mg/dL	0.60	0.87 mg/dL
	180 mg/dL	2.07	44.0%
Glucose	500 mg/dL	0.59	0.27 mg/dL
	500 mg/dL	2.09	11.5%
	1000 mg/dL	0.59	0.51 mg/dL
	1000 mg/dL	2.09	22.5%
Hydroxocobalamin (Cyanokit)	500 mg/L	0.62	0.22 mg/dL
	500 mg/L	2.14	14.5%
	2259 mg/L	0.59	1.13 mg/dL
	2259 mg/L	2.07	49.3%
Total Protein	15 g/dL	0.65	0.45 mg/dL

Urine

Human urine pools were split into control and test pools. The test pools were spiked with the interferents, and the control pools were spiked with an equivalent volume of the compound the interferent was prepared in. For urine samples, the low creatinine concentration (40.00 mg/dL) samples and the high creatinine concentration (180.00 mg/dL) samples were unique native human urine samples. Five replicates were tested per sample. Substances identified with > 10% bias were considered to have interfered. 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 was observed.

The table below lists the highest concentrations of each substance at which no significant interference was found in Urine.

Substance	Highest concentration tested that showed no interference
Ascorbate	3.0 mg/dL
Conjugated Bilirubin	50 mg/dL
Gamma Globulin	0.5 g/dL
Glucose	2000 mg/dL
Hemoglobin	100 mg/dL
Human Serum Albumin	0.5 g/dL
N-Acetyl Cysteine	2 mg/dL
6N HCL	0.01%
6N Nitric Acid	0.60%
Acetaminophen	200 mg/dL
Acetic Acid	25 mL/24-hr collection
Boric Acid	1% w/v
Ethanol	1 g/dL
Ibuprofen	500 mg/dL
Oxalic Acid	0.1 g/dL
pH 4	pH 4
pH 9	pH 9
Sodium Carbonate	5 g/24-hr collection
Cefoxitin	3300 mg/L
Levodopa	700 mg/L

Interference beyond $\pm 10\%$ for Urine

Substance	Substance Concentration	Analyte concentration (mg/dL)	Bias
Cefoxitin	4950 mg/L	42.55	11.3%
	6600 mg/L	42.55	15.4%

Limitations:

The sponsor included the following limitation statements in their instructions for use:

- Use of assay is not recommended for patients taking Cefoxitin. Cefoxitin may produce falsely increased results.
- The Atellica CH Crea3 assay is susceptible to interference from cephalosporin class antibiotics at therapeutically relevant interferent concentrations.

4. Assay Reportable Range:

The Atellica® CH Creatinine_3 (Crea3) assay reportable range on the Atellica® CH Analyzer is 0.15 mg/dL to 30.00 mg/dL for serum/plasma, and 3.00 mg/dL to 245.00 mg/dL for urine.

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

The Atellica® CH Chemistry Calibrator (CHEM CAL) is traceable to NIST SRM 967.

On-board Reagent Stability:

An open bottle stability study was conducted to ensure the reagent performed consistently throughout the claimed in use/onboard stability. The study results support the claim of on-board stability of 17 days. All protocols and results were reviewed and found to be acceptable.

Sample Stability

A sample stability study was conducted to establish the recommendations for the handling of patient samples specified in the Atellica® CH Creatinine_3 (Crea3) assay Instructions for Use. Study protocols and results for serum and urine sample stability were reviewed and found to be acceptable.

Calibration Interval:

The calibration interval study completed confirmed the lot calibration interval (defines the time the Atellica® CH Analyzer can store a fresh pack calibration) of 180 days and pack calibration interval (defines the time before re-calibration is required within an opened reagent pack chamber (well-set)) of 10 days. The protocol and acceptance criteria were reviewed and found to be acceptable.

6. Detection Limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and the Limit of Quantitation (LoQ) of the Atellica® CH Creatinine_3 (Crea_3) on the Atellica® CH Analyzer were evaluated in accordance with CLSI EP17-A2. The LoQ was defined as the lowest concentration of creatinine at which the total analytical error is ≤ 0.10 mg/dL for serum and plasma and ≤ 1.50 mg/dL for urine. A brief protocol and the results are summarized in the tables below:

Atellica® CH Creatinine_3 (Crea_3) - Limit of Detection Results (Serum/Plasma)		
Limit	Protocol	Value obtained
LoB	4 samples with no analyte were tested in 5 replicates per sample, one run per day for 3 days, 3 reagent lots	0.05 mg/dL
LoD	5 low analyte samples were tested in 5 replicates per sample one run per day for 3 days, 3 reagent lots	0.10 mg/dL
LoQ	5 low samples were tested in 5 replicates per sample one run per day for 3 days, 3 reagent lots	0.15 mg/dL

Atellica® CH Creatinine_3 (Crea_3) - Limit of Detection Results (Urine)		
Limit	Protocol	Value obtained
LoB	4 samples with no analyte were tested in 5 replicates per sample, one run per day for 3 days, 3 reagent lots	0.50 mg/dL
LoD	5 low analyte samples were tested in 5 replicates per sample one run per day for 3 days, 3 reagent lots	1.0 mg/dL
LoQ	5 low samples were tested in 5 replicates per sample one run per day for 3 days, 3 reagent lots	3.00 mg/dL

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The accuracy of the Atellica® CH Creatinine_3 (Crea3) assay on the Atellica® CH analyzer for serum and urine was evaluated for agreement with the predicate device by a method comparison study. The method comparison study was performed following the recommendations in CLSI EP09c-Ed3. A total of 151 serum samples (13 of the 151 samples were spiked) and 113 native urine samples were tested on the predicate device and on the candidate device. These samples were tested on one Atellica® CH Analyzer in silicate for both assays. Weighted Deming statistics were used to calculate the regression equations below:

Specimen Type	Comparison Assay (x)	Regression Equation	Sample Range as determined by comparator device (mg/dL)	N	r
Serum	Atellica CH Creatinine_2 (Crea_2)	$y = 1.00x - 0.04 \text{ mg/dL}$	0.44 - 28.64	151	1.000
Urine	Atellica CH Creatinine_2 (Crea_2)	$y = 1.00x + 0.14 \text{ mg/dL}$	12.60 - 237.06	113	1.000

2. Matrix Comparison:

The specimen equivalency was determined using the Weighted Deming regression. A total of 50 four-way matched sample sets (serum, lithium heparin plasma, sodium heparin plasma and EDTA plasma) were processed and tested with N= 1 replicate. The following results were obtained:

Specimen (y)	N	Reference Specimen (x)	Regression Equation	Sample Range mg/dL	r
Sodium Heparin	50	Serum	$y = 1.00x + 0.00 \text{ mg/dL}$	0.60 – 27.26	0.999
Lithium Heparin	50	Serum	$y = 0.99x + 0.06 \text{ mg/dL}$	0.60 - 27.26	0.999
Dipotassium EDTA	50	Serum	$y = 0.98x + 0.04 \text{ mg/dL}$	0.60 - 27.26	0.998

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 sponsor provided the following information for the reference ranges in serum and urine for the Atellica® CH Creatinine_3 (Crea3) assay:

Group	Sample Type	Reference Interval
Males	Serum	0.70 - 1.30 mg/dL (62 – 115 µmol/L)
Females	Serum	0.55 - 1.02 mg/dL (49 – 90 µmol/L)
Males	Urine	950 – 2490 mg/day (8.4 – 22.0 mmol/day)
Females	Urine	600-1800 mg/day (5.3 – 15.9 mmol/day)

Junge W, Wilke B, Halabi A, Klein G. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffé method.

Clin Chim Acta. 2004;344(1-2):137-48.

Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. Philadelphia, PA: WB Saunders Co; 1999:1809.Conclusions.

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.