510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K212223

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

Atellica® CH Enzymatic Creatinine_3 (ECre3)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JFY	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, enzymatic

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Atellica® CH Enzymatic Creatinine_3 (ECre3) assay is for in vitro diagnostic use in the quantitative determine of creatinine in human serum, plasma (lithium heparin and dipotassium EDTA), 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/Trinidad CH System

IV Device/System Characteristics:

A Device Description:

The Atellica® CH Enzymatic Creatinine_3 (ECre3) assay reagents are packaged in 2 packs with 2 wells per pack. The wells have a divider which keeps the two liquid chambers separate. In pack 1 (P1) and pack 2 (P2) both wells are used.

Atellica® CH ECre3 Pack 1 (P1) consist of 23.5 mL of Creatinase (<133,350 U/L); sarcosine oxidase(<39,000 U/L); N-ethyl-N-(3-methylphenyl)-N'-succinyl-ethylenediamine (EMSE)(0.04%); detergent; preservatives, bovine serum albumin (0.1%), bovine catalase.

Atellica®CH ECre3 Pack 2 (P2) consist of 11.5 mL of Peroxidase; creatininase(<600,000 U/L); 4-aminoantipyrine (4-AA) (0.001%); detergent; sodium azide (< 0.1%); preservatives.

B Principle of Operation:

This assay uses a creatinine enzymatic method that measures the concentration of creatinine through a series of coupled enzymatic reactions. A "pretreatment" reaction removes endogenous creatine and sarcosine using creatinase and sarcosine oxidase. First, creatinine is enzymatically converted by creatininase into creatine. Creatine is then enzymatically converted to sarcosine by creatinase. This is followed by the oxidation of sarcosine by sarcosine oxidase to produce hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide allows for the oxidative condensation of 4-aminoantipyrine and N-ethyl-N-(3-methylphenyl)-N'-succinylethylenediamine to produce a reddish purple quinone pigment. The absorbance of this quinone pigment is measured as an endpoint reaction at 545/694 nm.

V Substantial Equivalence Information:

A Predicate Device Name(s):

ADVIA Chemistry Enzymatic Creatinine_2

B Predicate 510(k) Number(s):

K070727

C Comparison with Predicate(s):

Device & Predicate Device(s):	K212223	K070727
Device Trade Name	Atellica® CH Enzymatic Creatinine_3 (ECre3)	ADVIA Chemistry Enzymatic Creatinine_2 (ECre_2)
General Device Characteristic Similarities		
Intended Use/Indications For Use	For in vitro diagnostic use in the quantitative determination of creatinine in human serum, plasma (lithium heparin and potassium EDTA), and urine. Such measurements are used in the diagnosis and treatment of renal diseases and in monitoring renal dialysis.	Same
Assay Principle	Enzymatic	Same
Sample Type	Serum, plasma (lithium heparin and K2 EDTA), urine	Same
General Device Characteristic Differences		
Assay Range	Serum/Plasma: 0.15–30.00 mg/dL Urine: 2.00–245.00 mg/dL	Serum/Plasma: 0.10–30.00 mg/dL Urine: 1.00–245.00 mg/dL

Calibrators	Atellica CH Chemistry Calibrator (CHEM CAL)	ADVIA Chemistry Calibrator (K050374)

VI Standards/Guidance Documents Referenced:

- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline–Third Edition. (CLSI EP05-A3).
- Interference Testing in Clinical Chemistry (CLSI EP07-ED3).
- Measurement Procedure Comparison and Bias Estimation Using Patient Samples (CLSI EP09c-ED3).
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline–Second Edition (EP17-A2).
- Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (CLSI EP25-A).
- Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition (CLSI EP28-A3c).
- Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking (CLSI EP34-ED1)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Eleven (11) samples comprised of 8 serum and 3 urine sample pools were aliquoted and frozen prior to the start of the study. Testing was performed with three (3) Atellica® CH ECre3 reagent lots on one (1) Atellica® CH Analyzer. For each testing day, new serum and urine pool aliquots were thawed and assayed. Each sample was assayed in two (2) replicates per run, with two (2) runs per day separated by a minimum of 2 hours between runs, for 20 days, yielding a total 80 replicates. Reproducibility was determined in accordance with CLSI EP05-A3 guideline. Samples were assayed n=5 in 1 run for 5 days using 3 instruments and 3 reagent lots. The data were analyzed to calculate the following components of precision: repeatability, between-day, between-lot, between-instrument, and reproducibility (total). The following results were obtained:

Precision summary results

Specimen Type	N	Mean mg/dL	Repeatability		Within-Lab	
			SD mg/dL	CV (%)	SD mg/dL	CV (%)
Serum 1 (Diluted)	80	0.41	0.009	2.2	0.013	3.2
Serum 2 (Native)	80	0.75	0.008	1.1	0.015	2.0
Serum 3 (Spiked)	80	1.29	0.010	0.8	0.030	2.3
Serum 4 (QC 1)	80	1.91	0.012	0.6	0.024	1.3
Serum 5 (QC 2)	80	3.11	0.009	0.3	0.026	0.8

Specimen Type	N	Mean mg/dL	Repeatability		Within-Lab	
			SD mg/dL	CV (%)	SD mg/dL	CV (%)
Serum 6 (Spiked)	80	8.89	0.021	0.2	0.055	0.6
Serum 7 (Spiked)	80	18.52	0.039	0.2	0.093	0.5
Serum 8 (Spiked)	80	26.49	0.054	0.2	0.121	0.5
Urine 1	80	42.82	0.064	0.1	0.322	0.8
Urine 2	80	86.41	0.156	0.2	0.497	0.6
Urine 3	80	185.06	0.320	0.2	0.831	0.4

Reproducibility Summary results

Specimen Type	N	Mean mg/dL	Repeatability		Between-Day		Between-Lot		Between Instrument		Total Reproducibility	
			SD mg/dL	CV (%)	SD mg/dL	CV (%)	SD mg/dL	CV (%)	SD mg/dL	CV (%)	SD mg/dL	CV (%)
Serum 1	225	0.44	0.008	1.9	0.005	1.1	0.008	1.9	0.000	0.0	0.013	2.9
Serum QC 1	225	0.79	0.011	1.3	0.004	0.5	0.008	1.0	0.000	0.0	0.014	1.7
Serum 2	225	0.95	0.014	1.4	0.034	3.5	0.000	0.0	0.007	0.7	0.037	3.9
Serum QC 2	225	1.88	0.011	0.6	0.008	0.4	0.009	0.5	0.000	0.0	0.016	0.8
Serum QC 3	225	6.82	0.016	0.2	0.022	0.3	0.000	0.0	0.017	0.2	0.032	0.5
Serum 3	225	7.96	0.021	0.3	0.034	0.4	0.000	0.0	0.019	0.2	0.045	0.6
Serum 4	225	26.86	0.051	0.2	0.105	0.4	0.039	0.1	0.082	0.3	0.148	0.6
Urine 1	225	42.30	0.106	0.2	0.102	0.2	0.000	0.0	0.171	0.4	0.225	0.5
Urine 2	225	189.56	0.379	0.2	0.401	0.2	0.503	0.3	1.024	0.5	1.267	0.7

2. Linearity:

A linearity study was performed following the recommendations in the CLSI EP6-A guideline.

Native human serum and native human urine samples were spiked to create the high samples. Native human serum and native human urine were diluted with Atellica® CH Diluent to create the low samples. A set of 8 equally spaced creatinine sample levels were prepared by mixing a low serum/urine sample with a high serum/urine sample.

The expected creatinine concentration levels used in the study for serum: 0.01, 3.93, 7.84, 11.75, 15.66, 19.58, 23.49, 27.40, and 31.31 mg/dL and for urine: 0.28, 32.34, 64.48, 96.58, 128.68, 160.78, 192.88, 224.98, and 257.07 mg/dL. Measurements were made with 4 replicates per level. The results showed that the deviation from linearity did not exceed 5%. The results of the regression analysis are summarized below:

Analyte	Sample Type	Linear Regression
Creatinine	Serum	y=0.99x+ 0.02 mg/dL
	Urine	y=0.98x + 0.05 mg/dL

The results from the linearity study support an analytical measuring range of 0.15 to 30.00 mg/dL for serum/plasma and 2.00 to 245.00 mg/dL for urine.

Dilution:

The sponsor provided data to support that automatic dilution can be used to assay samples containing creatinine concentrations above the claimed analytical measuring interval. The results of the dilution study showed that 5-fold dilution could be used to measure samples within an extended measuring interval up to 150.00 mg/dL for the serum/plasma sample type and up to 1225.00 mg/dL for the urine sample type using the automated dilution routine on the Atellica® Chemistry Analyzer.

3. Analytical Specificity/Interference:

The interference study was performed following the recommendations in the CLSI EP07-3rd edition guideline.

Various concentrations of interferents were spiked into pooled human serum or pooled human urine containing creatinine at normal (1 mg/dL) and high (8 mg/dL) concentrations. Human serum 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 diluent. Low level analyte serum pool was native serum and the high-level analyte serum pool was prepared using a concentrated creatinine spiking solution. Five (5) replicates were tested per sample. Nonsignificant interference was defined by the sponsor as the highest interferent level tested with ≤10% bias of the control for both serum and urine samples.

Serum Creatinine:

Test Interferent	**Highest concentration tested that showed no interference**
Hemoglobin	200 mg/dL
Lipema	2000 mg/dL
Conjugated Bilirubin	25 mg/dL
Unconjugated Bilirubin	25 mg/dL
Acetaminophen	200 µg/mL
N-Acetylcysteine (NAC)	37.5 mg/dL
N-acetyl-p-benzoquinine imine (NAPQI)	0.4 mg/dL
Methyldopa	22.5 µg/mL
L-Dopa	15 µg/mL
Calcium Dobesilate	0.375 mg/dL
Cefoxitin	6600 µg/mL
Cephalexin	200 µg/mL
Dicynone (Etamsylate)	0.59 mg/dL
DL-proline	11.5 mg/dL
Dobutamine	5 µg/mL
Dopamine	10 µg/mL
Ethylglycine (N-ethylglycine)	6 µg/mL
Fluorocytosine	200 µg/mL
Metamizole (Sulpyrine)	25 mg/dL
Phenindione	4 mg/dL

Test Interferent	Highest concentration tested that showed no interference
Phenylbutazone	321 µg/mL
Rifampicin	2.4 mg/dL
Salicylate	200 µg/mL

The sponsor noted that published literature has shown that in very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results. The package insert contains the following limitation: "Blood samples from some patients with monoclonal gammopathies may produce falsely elevated results."

Urine Creatinine:

Test Interferent	Highest concentration tested that showed no interference
6N HCl	0.01% HCL
pH 4	4.0 pH
pH 9	9.0 pH
Acetaminophen	200 mg/dL
Acetic Acid	25 mL/24 hr collection
Albumin	0.5 g/dL (5 g/L)
Ascorbate	3.0 mg/dL (199.9 µmol/L)
Boric Acid	1% w/v
Conjugated Bilirubin	50 mg./dL (855 µmol/L)
Ethanol	1 g/dL (216.9 mmol/L)
Gamma Globulin	0.5 g/dL (5 g/L)
Glucose	2000 mg/dL (111.1 mmol/L)
Hemoglobin	100 mg/dL (0.1 g/L)
Ibuprofen	500 mg/dL (24.3 mmol/L)
N-Acetyl cysteine	2 mg/dL (122/6
Nitric Acid	0.6%
Oxalic Acid	0.1 g/dL (11.1 mmol/L)
Sodium carbonate	5 g/24 hr collection

4. Assay Reportable Range:

   Serum/Plasma:

   0.15 – 30.00 mg/dL

   Urine:

   2.00 – 245 mg/dL

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

   The assay is traceable to the National Institute of Standards and Technology (NIST) Standard Reference Material SRM 967.

Additionally, 47 serum samples with creatinine concentrations across the assay range were tested on Isotope Dilution Mass Spectrometry (IDMS) to demonstrate alignment of the assay with this reference procedure.

Specimen Type	Comparison Assay	N	R	Regression Equation	Sample Range (mg/dL)
Serum	IDMS	47	0.991	y=1.01x + 0.01	0.35-26.70

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined in accordance with CLSI EP17-A2 guideline.

For the LoB determination of serum and urine, 4 blank samples were tested with n=5 replicates per sample using 3 Atellica® CH ECre3 reagent lots for 3 days on 1 Atellica CH Analyzer for a total of 60 measurements per reagent lot. The LoB was calculated non-parametrically as the 95th percentile ranked position of all blank samples.

The LoD was determined parametrically using the pooled standard deviation of the highest observed LoB and results from 4 low analyte serum and urine samples prepared by diluting native serum and urine samples with Atellica® CH Diluent and tested in n=5 replicates per sample using 3 Atellica® CH ECre3 reagent lots for 3 days on 1 Atellica® CH Analyzer for a total of 60 measurements per reagent lot.

A LoQ study was performed using 4 low concentration serum pools and 2 reagent lots. Each sample was assayed in n=5 replicates per sample on 3 Atellica® CH ECre3 reagent lots for 3 days, on 1 Atellica® CH Analyzer for a total of 60 measurements per lot for serum and urine, respectively. 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. The results are summarized in the table below:

Matrix	LoB (mg/dL)	LoD (mg/dL)	LoQ (mg/dL)
Serum	0.02	0.04	0.13
Urine	0.07	0.19	1.93

The studies support the lower limits of assay range claims for serum (0.15 mg/dL) and urine (2.00 mg/dL) and the following detection limit claims in the labeling:

Matrix	Detection Capability	Result (mg/dL)
Serum/Plasma	LoB	0.05
	LoD	0.10
	LoQ	0.15
Urine	LoB	0.15
	LoD	0.50
	LoQ	2.00

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Method comparison studies were conducted consistent with CLSI EP09C-ED3 guideline.

Native patient samples (serum N= 105, urine N=102) were used in these studies. Each sample was assayed in duplicate using the candidate method Atellica® CH ECre3 reagent tested on one Atellica® CH Analyzer and the predicate method ADVIA Chemistry ECRE_2 tested on one ADVIA 1800 Chemistry system. Only the first replicate was used for analysis.

Deming regression results are as follows:

Matrix	N	Claimed measuring range (mg/dL)	Ranges of samples as determined by Predicate (mg/dL)	Regression Equation (mg/dL)	R
Serum	105	0.15-30	0.18-28.41	y=0.99x + 0.02	1.000
Urine	102	2.00-245	4.71-240.47	y=0.98x + 0.05	0.999

2. Matrix Comparison:

Fifty-five (55) matched samples (serum, lithium heparin plasma, and K2-EDTA plasma) were evaluated in duplicate with 1 lot of the Atellica® CH ECre3 reagent. Five (5) of the samples were spiked to obtain higher creatinine concentrations. Only the first replicate was used in analysis.

Deming regression results are as follows:

Matrix Y	Matrix X	N	Claimed measuring range (mg/dL)	Ranges of samples (mg/dL)	Regression Equation (mg/dL)	R
Lithium Heparin Plasma	Serum	55	0.15-30	0.50-26.91	y=0.99x + 0.00	1.000
K2-EDTA Plasma	Serum	55	2.00-245	0.50-26.91	y=0.97x + 0.02	0.999

The results of the study support the sponsor's claim that lithium heparin and K2-EDTA plasma are acceptable sample types for the candidate device.

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:

Expected Values

Transference as defined in CLSI EP28-A3c was used to verify established reference ranges for serum and plasma creatinine. Healthy male and female serum, lithium heparin plasma, and dipotassium EDTA plasma samples were obtained (23 men and 21 women) and processed with N=2 replicates, only the first replicate was used in analysis. Results of the verification study support the serum reference ranges which were established through literature.

Group	Sample Type	Reference Interval
Males	Serum/Plasma[a]	0.73-1.18 mg/dL
Females	Serum/Plasma[a]	0.55-1.02 mg/dL
Males	Urine[b]	800-2000 mg/day
Females	Urine[b]	600-1800 mg/day

[a] 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.

[b] Wu, AHB. Tietz Clinical Guide to Laboratory Tests. 4th ed. Philadelphia, PA: WB Saunders Company; 2006:316..

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.