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

A. 510(k) Number:

k161494

B. Purpose for Submission:

New Device

C. Measurand:

Creatinine

D. Type of Test:

Quantitative, photometric/colorimetric method

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Atellica CH Creatinine_2 (Crea-2)

Atellica CH Chemistry Calibrator (CHEM CAL)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CGX	II	21 CFR 862.1225, Creatinine test system	Chemistry (75)
JIT	II	21 CFR 862.1150, Calibrator	Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   The Atellica™ CH Creatinine_2 (Crea_2) assay is an in vitro diagnostic test used for the quantitative measurement of creatinine in human serum, plasma (lithium heparin), and urine, using the Atellica™ CH Analyzer. Creatinine measurements are used in the diagnosis and treatment of certain renal diseases, and in monitoring renal dialysis patients.

   The Atellica™ CH Chemistry Calibrator (CHEM CAL) is used for calibrating the Crea_2 assay using the Atellica™ CH Analyzer.

3. Special conditions for use statement(s):

   For Prescription use only.

4. Special instrument requirements:

   Atellica™ CH Analyzer

I. Device Description:

Atellica CH Crea_2 reagents has 2 major reagent packs. Reagent pack 1 (P1) contains 34.0 mL of sodium hydroxide (0.8) mol/L, and reagent pack 2 (P) contains 44.6 ml of picric acid (25 mmol/L).

The Atellica CH Chemistry Calibrator (CHEM CAL) is a one level lyophilized calibrator formulated from a bovine serum base product. The calibrator is supplied as a pack of 12 vials; each will hold 3ml after reconstitution.

All human sources materials were tests by FDA approved methods and found to be negative for HIV-1, HIV-2, and HBsAg.

The Atellica CH Analyzer has been previously cleared as the Trinidad CH System under k151767; the new name of the system is the Atellica CH Analyzer.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Chemistry Enzymatic Creatinine_2 (ECRE-2)
   ADVIA Chemistry Calibrator

3. Predicate 510(k) number(s):
   k070727
   k050374

4. Comparison with predicate:

Assay:

Similarities/Differences		
Item	k161494 Atellica CH Creatinine_(Crea_2)2 Candidate Device	k070727 ADVIA Chemistry Enzymatic Creatinine_2 (ECRE_2) Predicate Device
Intended Use :	Is intended for the quantitative measurement of creatinine in human serum, plasma (lithium heparin), and urine.	Same
Device Technology:	Modified Jaffe methodology (creatinine alkaline picrate) with photometric detection.	Enzymatic reaction of Fossati, Prencipe, and Berti
Sample Type:	Serum, Lithium Heparin Plasma and urine	Serum, Lithium Heparin plasma, K_2EDTA plasma and urine
Reference Interval:	Serum/plasma Males 0.70-1.30 mg/dL Females 0.55 -1.02 mg/dL Urine: Males 950 – 2490 mg/day Females 600 – 1800 mg/day	Serum/Plasma: Males 0.6 – 1.1 mg/dL Females 0.5 – 0.8 mg/dL Urine Males 800 – 2000 mg/day Females 600 – 1800 mg/day
Standardization:	IDMS Reference Method	SRM967
Calibration Frequency:	60 days	Same
Analytical Measuring Range	Serum and plasma: 0.15–30.00 mg/dL Urine: 3.00–245.00 mg/dL	Serum/Plasma: 0.10 – 30.00 mg/dL Urine: 1.0 – 245.00 mg/dL
Interferences	Bilirubin (Unconjugated) – 10 mg/dL Bilirubin (Conjugated) – 20 mg/dL (Intralipid®) – 500 mg/dL Hemoglobin – 500 mg/dL	Bilirubin (Unconjugated) – 30 mg/dL Bilirubin (Conjugated) – 30 mg/dL Lipemia (Intralipid®) – 100 mg/dL Hemoglobin – 500 mg/dL

Calibrator:

Similarities/Differences		
Item	k161494 Atellica CH Chemistry Calibrator (CHEM CAL) candidate Device	k050374 ADVIA Chemistry Calibrator Predicate Device
Intended Use :	Is intended for *in vitro* diagnostic use in calibrating the Creatinine assay.	Same
Calibrator Matrix:	Bovine Serum Base	Same
Calibrator Form:	Lyophilized	Same
Number of Calibrator Levels:	One	Same
Value assignment	Traceable to IDMS Reference Method and NIST SRM 914	Traceable to NIST SRM914

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

The following guidelines from the Clinical and Laboratory Standards Institute (CLSI) were referenced:

- EP07-A2: Interference Testing of Clinical Chemistry; Approved Guideline
- EP09-A3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples: Guideline - Third Edition
- EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline
- EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures
- EP25-A: Evaluation of Stability of *In Vitro*Diagnostic Reagents; Approved Guideline
- EP28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition

L. Test Principle:

The Atellica™ CH Creatinine_2 (Crea_2) assay is used to measure the creatinine concentration in human serum, plasma (lithium heparin), and urine using the Atellica™ CH Analyzer. The technique used 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. 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

All performance studies were performed on the Atellica™ CH Analyzer.

a. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI EP05-A3. Testing was performed two times a day in 2 replicates for 20 non-consecutive days for a total of 80 replicates. This study was performed using 3 serum pools with mean concentration values of 1.16 mg/dL, 19.31 mg/dL, and 26.00 mg/dL, 2 serum QC samples with mean concentration values of 1.97 mg/dL and 6.35 mg/dL,1 serum sample with a mean concentration value 0.38 mg/dL and 1 plasma pool with a mean concentration value of 0.66 mg/dL. The urine precision study was performed using 2 levels of urine QC samples with mean concentration values of 59.62 mg/dL and 133.31 mg/dL, and 1 urine pool sample with a mean concentration value of 188.61 mg/dL. The results are summarized as below:

Sample Type	n	Mean mg/dL (µmol/L)	Repeatability		Within-Lab Precision	
			SD mg/dL (µmol/L)	CV (%)	SD mg/dL (µmol/L)	CV (%)
Serum	80	0.38 (34)	0.01 (0.5)	1.7	0.010 (0.9)	2.8
Plasma pool	80	0.66(58)	0.01 (0.7)	1.2	0.018 (1.6)	2.8
Serum Pool	80	1.16 (103)	0.01 (0.9)	0.8	0.017(1.5)	1.5
Serum QC	80	1.97 (174)	0.02 (1.6)	0.9	0.024 (2.1)	1.2
Serum QC	80	6.35 (561)	0.04 (3.7)	0.7	0.062 (5.5)	1.0
Serum Pool	80	19.31 (1707)	0.04 (3.4)	0.2	0.117 (10.3)	0.6
Serum Pool	80	26.00 (2298)	0.05 (4.7)	0.2	0.145 (12.8)	0.6
Urine QC	80	59.62 (5270)	0.15 (13.5)	0.3	0.376 (33.2)	0.6
Urine QC	80	133.31 (11785)	0.33 (29.4)	0.2	0.961 (85.0)	0.7
Urine	80	188.61 (16673)	0.52 (46.1)	0.3	1.779 (157.3)	0.9

b. Linearity/assay reportable range:

A linearity study was performed in accordance with CLSI EP06-A. Samples were prepared by mixing high and low concentration samples to span the measurement interval; 12 samples were used to evaluate the entire measuring interval for serum and 10 samples were used to evaluate the entire measuring interval for 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 0.09 - 32.58 ng/dL and the concentrations for urine samples ranged from 0.20 - 278.43 mg/dL.

The regression statistics of the serum linearity study:
Y = 1.004x + 0.085, r = 1.000

The regression statistics of the urine linearity study:
Y = 0.986x + 0.049, r = 0.999

The results of the linearity studies support the claimed measuring intervals for 0.15-30.00 mg/dL for serum and plasma specimens and 3.00-245.00 mg/dL for urine samples for the Atellica CH Creatinine_2 (Crea_2) assay on the Atellica™ CH Analyzer.

Validation of the automatic dilution function has been performed and the extended reportable range for serum is determined to be 60 mg/dl for serum and 735 mg/dL in urine. Both sample types have been shown to be accurately diluted (manually or by auto-dilution) in this range.

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

Traceability:

The Atellica CH Chemistry Calibrator (CHEM CAL) is traceable to NIST SRM 914 via value assignment (see below).

Additionally 49 serum samples were tested across the assay range were tested on Isotope Dilution Mass Spectrometry (IDMS) to demonstrate standardization of the assay.

Specimen type	Comparison Assay (x)	N	R	Regression Equation	Sample Range
Serum	IDMS	49	0.999	y=0.96x + 0.05	0.41 – 32.09 mg/dL

Manufacturing and value assignment for the calibrator:

The calibrator is manufactured with a bovine serum albumin base. Assigned lot-specific calibrator values used for the ADVIA Chemistry Calibrator will be utilized for the calibration of Atellica CH Creatinine_2 assay on the Atellica CH Analyzer. The target assigned value range is 7.6 to 9.6 mg/dL. A master lot is created and values are assigned on an ADVIA Chemistry system calibrated with NIST SRM 914; the master lot is used to assign the values of the commercial lots. The % recovery of the commercial lot is compared to the % recovery of the Master Lot and the previously released lot. The % recovery error limit is ±5%. The imprecision limit is 2.0% CV.

Stability: All studies were completed in accordance with CLSI EP25-A, *Evaluation of Stability of In Vitro Diagnostic Reagents*.

Reagent Stability:

The 12 month shelf claim was established by an accelerated stability study. A real time stability study to support a claim of 12 months shelf life is ongoing. Unopened product is stable until the expiration date on the product stored at 15-25^{0}C. All protocols and acceptance criteria were reviewed and found acceptable.

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 at 15-25^{0}C. All protocols and acceptance criteria were reviewed and found to be acceptable.

Calibrator Stability:

The shelf life of the unopened vial of calibrator is 24 months when stored at 2-8^{0}C. Open vial/onboard calibrator is stable for 48 hours at 2-8^{0}C. All protocols and acceptance criteria were reviewed and found acceptable.

Calibration Interval:

The calibration interval was evaluated in studies completed in accordance with CLSI EP25-A. The study completed confirmed the calibration interval of 60 days. The protocol and acceptance criteria were reviewed and found to be acceptable.

d. Detection limit:

The Limit of Blank (LoB) and Limit of Detection (LoD) and the Limit of Quantitation(LoQ) of the Atellica CH Creatinine_2 (Crea_2) on the Atellica CH Analyzer were evaluated in accordance with CLSI EP17-A2. A brief protocol summary and the results are presented in the table below:

Atellica CH Creatinine_2 (Crea_2) - Limit of Detection Results (Serum/Plasma)		
Limit	Protocol	Value obtained
LoB	4 samples with no analyte were tested 5 times for 3 days, one run per day, 3 reagent lots	0.03 mg/dL
LoD	4 low analyte samples were tested 5 times for 3 days, one run per day, 3 reagent lots	0.08 mg/dL
LoQ	5 replicates of ten low samples on three reagent lots for three days.	0.13mg/dL

Atellica CH Creatinine_2 (Crea_2) - Limit of Detection Results (Urine)		
Limit	Protocol	Value obtained
LoB	4 samples with no analyte were tested 5 times for 3 days, one run per day, 3 reagent lots	0.35 mg/dL
LoD	4 low analyte samples were tested 5 times for 3 days, one run per day, 3 reagent lots	0.51 mg/dL
LoQ	5 replicates of ten low samples on three reagent lots for three days.	2.57mg/dL

The values obtained from this study support the claimed LoQ for serum creatinine of 0.13mg/dL and LoD of 0.08 mg/dL. The LoQ for urine creatinine is 2.57 mg/dL and the LoD is 0.51 mg/dL.

e. *Analytical specificity:*

The evaluation of potential interferents followed the recommendations in CLSI EP7-A2. Interference studies were performed for the creatinine measurement function by evaluating potential interfering substances using a "paired difference worst case scenario" approach, where interfering compounds were spiked at low or high levels into fresh serum or urine sample pools. Bias was defined as the difference in results between the control samples (without the interferent) and the test sample (containing the interferent) expressed in percent; results with a bias exceeding 10% was considered interference. Dilution studies were conducted to determine the level at which the spiked substance no longer displayed significant interference.

No significant interference was detected for these endogenous substances at the following Concentrations in serum :

Substance in Serum	Minimum concentration tested without interference
Hemoglobin	500 mg/dL
Bilirubin, conjugated	20 mg/dL
Bilirubin, unconjugated	10 mg/dL
Lipemia (Intralipid)	500 mg/dL

The following exogenous substances showed less than 10% bias in the Crea_2 assay in serum.

Substance in Serum	Minimum concentration Interference
Glucose	182 mg/dL
Ascorbate	3.0 mg/dL
Total Protein	11.7 g/dL
Total Protein	12.0 g/dL
Cefoxitin	3.75 mg/dL
Cefoxitin	5 mg/dL
Cephalexin	25 mg/dL
Pyruvate	7.5 mg/dL
Acetoacetate	20 mg/dL
Potassium Oxalate	500 mg/dL
Dopamine (LevaDopa)	75 mg/dL
Albumin Serum	6000 mg/dL
Amikacin	8 mg/dL
Caffiene	6 mg/dL
Carbamazepine	3 mg/dL
Cephradine	25 mg/dL
Chloramphenicol	5 mg/dL
Chlordiazepoxide	1mg/dL
Cimetidine	2 mg/dL
Dextran	6000 mg/dL
Diazepam	0.51 mg/dL
Digoxin	6.1 ng/mL
EDTA	200 mg/dL
Erythromycin	6 mg/dL
Ethanol - Serum	400 mg/dL
Ethosuximide	25 mg/dL
Furosemide	6 mg/dL
Gentamicin	1 mg/dL
IgG	5000 mg/dL
Isopropanol	1 g/dL
Lidocaine	1.2 mg/dL
Nicotine	0.10 mg/dL
Nortriptyline	1000 ng/mL

Substance in Serum	Minimum concentration Interference
Penicillin G(1654)	25 U/mL
Pentobarbital	8 mg/dL
Phenobarbital	10 mg/dL
Phenytoin	5 mg/dL
Primidone	4 mg/dL
Propoxyphene	0.16 mg/dL
Sodium Fluoride	400 mg/dL
Theophylline	4 mg/dL
Triglyceride	1500 mg/dL
Triglyceride	2500 mg/dL
Urea	500 mg/dL
Uric acid	20 mg/dL
Valproic Acid	50 mg/dL
Vancomycin	10 mg/dL

In Urine: Substances	Minimum concentration without interference
6N HCL @ 0.01%HCl	0.01% HCl
1% w/v Boric Acid	1% w/v
pH 4	pH 4
pH 9	pH 9
Ascorbate	3.0 mg/dL
Glucose	2000 mg/dL
Conjugated Bilirubin	50 mg/dL
Hemoglobin	100 mg/dL
Acetaminophen	200 mg/dL
N-Acetyl cysteine	2 mg/dL
Ibuprofen	500 mg/dL
Acetic Acid	25 mL/24 hr collection
Albumin - Urine	0.5 g/dL
Ethanol - Urine	1 g/dL
Gamma Globulin	0.5 g/dL
Nitric Acid	0.6 %
Oxalic Acid	0.1g/dL
Sodium carbonate	5 g/24 hr collection.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed following the recommendations in CLSI EP09-A3. A total of 143 serum samples and 109 urine samples were tested on the predicate device and on the candidate device, Atellica CH Creatinine_2 (Crea_2) assay on the Atellica CH Analyzer. Samples tested in the study included 10 spiked serum samples and 10 diluted urine samples to cover the lower end of the claimed assay ranges of 0.15-30 mg/dL (serum) and 3.00-245.00 mg/dL (urine). One replicate of each sample was tested on both test systems, and used in the analysis. Three of the serum samples were excluded from the analysis because they were below the predicate's measuring interval. Weighted Deming statistics were used to calculate the regression equation below:

Serum: $y = 0.98x + 0.0$ $r = 0.999$

Urine: $y = 0.95x + 0.07$ $r = 0.999$

b. Matrix comparison:

A total of fifty eight serum and lithium heparin plasma samples were tested on the Atellica CH Creatinine_2 (Crea_2) assay on the Atellica CH Analyzer. Seven samples were spiked with creatinine to cover the upper end of the claimed measuring range. One replicate of each sample was tested and used in the analysis.

The table below summarizes the weighted Deming linear regression statistics of the matrix comparison study

Specimen Type	Comparison Assay (x)	N	r	Regression Equation	Sample Range (mg/dL)
Plasma (Lithium heparin)	Atellica CH Crea_2 – Serum	58	1.000	y = 1.00x – 0.01	0.68 – 24.87

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:

Transference as defined in CLSI EP28-A3c was used to validate established reference ranges for serum and plasma creatinine. The sponsor performed a study to verify that the reference ranges, provided in literature and cited in the labeling, could be transferred to the candidate device. The study demonstrated that the published reference ranges could be transferred.

Group	Specimen type	Reference Interval common unit (SI unit)
Adult males	Serum/plasma[1]	0.70 - 1.30 mg/dL (62 - 115 µmol/L)
Adult females	Serum/plasma[2]	0.55 - 1.02 mg/dL (49 - 90 µmol/L)
Adult males	Urine[3]	950 - 2490 mg/day (8.4 - 22.0 mmol/day)
Adult females	Urine[4]	600- 1800 mg/day (5.3 - 15.9 mmol/day)

The expected ranges presented in the proposed package insert were established from scientific literature with references listed below.

1. Burtis CA, Ashwood ER, eds. *Tietz Fundamentals of Clinical Chemistry.* 5th ed. Philadelphia, PA:WB Saunders Co; 2001:23-25, 422.

2. Ceriotti F, Boyd JC, Klein G, *et al*. Reference intervals for serum creatinine concentrations: assessment of available data for global application. *Clin Chem.* 2008;54(3):559-566.

3. 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.

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

Published 24 hour urine reference intervals are recommended because of difficulty in obtaining 24 hr. urine samples. Siemens recommends that each laboratory should come up with their own reference intervals for the diagnostic evaluation of the patients results.

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.