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

A. 510(k) Number:
k070727

B. Purpose for Submission:
New Device

C. Measurand:
Creatinine

D. Type of Test:
Quantitative, enzymatic

E. Applicant:
Siemens Medical Solutions Diagnostics

F. Proprietary and Established Names:
Advia Chemistry Enzymatic Creatinine_2 (ECRE_2)

G. Regulatory Information:
   1. Regulation section:
      21 CFR § 862.1225 - Creatinine test system
   2. Classification:
      Class II
   3. Product code:
      JFY – Enzymatic Method Creatinine
   4. Panel:
      Clinical Chemistry (75)

H. Intended Use:
   1. Intended use(s):
      Refer to Indications for use below.

   2. Indication(s) for use:
      The ADVIA Chemistry Enzymatic Creatinine_2 is for in vitro diagnostic use in
      the quantitative determination of creatinine in human serum, plasma, and urine on
      the ADVIA Chemistry Systems. Such measurements are used in the diagnosis and
      treatment of renal diseases, and in monitoring renal dialysis.

   3. Special conditions for use statement(s):
      Prescription use only

   4. Special instrument requirements:
      For use with Siemens ADVIA 1200, ADVIA 1650 and ADVIA 2400 Chemistry
      Systems

I. Device Description:
   The ADVIA Chemistry Enzymatic Creatinine_2 assay is available as a kit only. It
   consists of 2 reagents. Reagent 1 contains Creatinase (75 U/ml), Sarcosine oxidase
   (20 U/ml), and N-(3-sulfopropyl)-3-methoxy-5-methylaniline (0.9 mmol/L). Reagent

2 contains creatininase (400 U/ml), 4-aminoantipyrine (6.1 mmol/L), and peroxidase (50 U/ml).

J. Substantial Equivalence Information:

1. Predicate device name(s):
ADVIA Chemistry Enzymatic Creatinine (CREA_E) and ADVIA Chemistry Creatinine_2 (CREA_2)

2. Predicate 510(k) number(s):
k991576 and k973993, respectively

3. Comparison with predicate:

Item	**New Device** ADVIA Chemistry Enzymatic Creatinine_2	**Predicate - k991576** ADVIA Chemistry Enzymatic Creatinine
Analyte	Creatinine	Creatinine
Method	Enzymatic (Creatininase)	Enzymatic (Creatinine Deiminase/GLDH)
Reagent components	Two liquid reagents: Reagent 1: Creatinase (75 U/ml), Sarcosine oxidase (20 U/ml), and N-(3-sulfopropyl)-3-methoxy-5-methylaniline (0.9 mmol/L); Reagent 2: Creatininase (400 U/ml), 4-aminoantipyrine (6.1 mmol/L), peroxidase (50 U/ml).	Two lyophilized reagents requiring reconstitution: Reagent 1: TRIS Buffer (150 mmol/L); Reagent 1 mix: NADPH (8 mg); 2-oxoglutarate (56.5 mg); GLDH > 2KU Reagent 2 mix: Creatinine deiminase (40 U)
Format	Liquid	Liquid
Calibration	Single point	Single point
Calibrator	Bayer Chemistry Calibrator (REF 09784096)	Bayer Chemistry Calibrator (REF 09784096)
Linearity/Assay range	Serum: 0.1 – 30.0 mg/dL Urine: 0.1 – 245 mg/dL	Serum: 0.0 - 30.0 mg/dL
Expected Values (Serum)	Males: 0.6 – 1.1 mg/dL Females: 0.5 – 0.8 mg/dL	Males: 0.9 – 1.3 mg/dL Females: 0.6 – 1.1 mg/dL
Expected Values (Urine)	Males: 800 - 2000 mg/day Females: 600 - 1800 mg/day	Not Applicable
Closed reagent stability	Until the expiration date when stored at 2-8°C	Until the expiration date when stored at 2-8°C
Open reagent (on-board) stability	60 days	21 days
Sample matrix	Plasma, serum, urine	Plasma, serum

K. Standard/Guidance Document Referenced (if applicable):
CLSI EP-5A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

Creatinine is converted to creatine by the action of creatininase. The creatine formed is hydrolyzed by creatinase to produce sarcosine, which is decomposed by sarcosine oxidase to form hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide formed yields a blue pigment by condensation with N-(3-sulfopropyl)-3-methoxy-5-methylaniline (HMMPS) and 4-aminoantipyrine. The creatinine concentration is obtained by measuring the absorbance of the blue color at 596/694 nm. The absorbance of the color is proportional to the creatinine concentration.

M. Performance Characteristics:

1. Analytical performance:

    a. *Precision/Reproducibility:*

        Precision was evaluated for both serum and urine following recommendations in CLSI EP-5A2. Studies were conducted at one site over 10-day period with each sample tested 2 times per run and 2 runs per day. Two levels of serum pools, 2 levels of serum-based controls, and 3 levels of urine control were tested. Precision was evaluated for 3 ADVIA instruments for which the results are given below.

        ADVIA 1200

Specimen	Level (mg/dL)	Within-Run SD	CV (%)	Total SD	CV (%)
Serum Pool	1.29	0.01	0.6	0.01	1.0
Control 1	1.73	0.01	0.8	0.02	1.1
Serum Pool	3.04	0.03	0.8	0.03	0.9
Control 2	8.79	0.06	0.6	0.08	0.9
Urine	42.34	0.30	0.7	0.41	1.0
Urine	79.78	0.78	1.0	0.91	1.1
Urine	133.09	1.22	0.9	1.34	1.0

ADVIA 1650

Specimen	Level (mg/dL)	Within-Run		Total	
		SD	CV (%)	SD	CV (%)
Serum Pool	1.29	0.01	0.8	0.01	1.1
Control 1	1.76	0.01	0.5	0.02	0.9
Serum Pool	3.07	0.03	0.8	0.03	1.1
Control 2	8.80	0.03	0.4	0.06	0.6
Urine	41.56	0.26	0.6	0.55	1.3
Urine	77.27	0.26	0.3	0.78	1.0
Urine	133.59	0.33	0.3	1.17	0.9

ADVIA 2400

Specimen	Level (mg/dL)	Within-Run		Total	
		SD	CV (%)	SD	CV (%)
Serum Pool	1.28	0.01	1.0	0.01	1.1
Control 1	1.75	0.01	0.7	0.01	0.8
Serum Pool	3.06	0.03	0.8	0.03	0.9
Control 2	8.81	0.10	1.1	0.12	1.4
Urine	41.13	0.15	0.4	0.41	1.0
Urine	77.54	0.18	0.2	0.69	0.9
Urine	131.33	0.40	0.3	1.23	0.9

b. Linearity/assay reportable range:

The sponsor reported linearity and reportable range data for ADVIA 1200, ADVIA 1650, ADVIA 1800 and ADVIA 2400 instruments. Two urine and serum sample pools (high and low) were used to prepare 9 equally spaced concentration levels for an approximate range of 3.5 – 30.0 mg/dL and 30 – 240 mg/dL, respectively. Each test level was run in duplicate on the above analyzers. Based on a linear regression analysis conducted for measured and assigned values, Enzymatic Creatinine_2 assay is linear within the entire range tested across the entire group of instruments evaluated. The sponsor's acceptance criterion is <5% difference between expected and observed values. The sponsor established the assay reportable range for urine at 1 – 245 mg/dL. Since the above study for serum did not include the values for expected levels of creatinine, (0.6-1.1 mg/dL), the study below was conducted to evaluate the assay reportable range for serum.

To evaluate the linearity of the assay within the expected levels of creatinine in serum (0.6-1.1 mg/dL), the sponsor used the College of American

Pathologists (CAP) Creatinine Linearity/Accuracy Panel (LN24-A) designed to evaluate the accuracy, calibration, and linearity of a creatinine assays in the normal and elevated range. The data demonstrated that Enzymatic Creatinine_2 method on ADVIA 1200, ADVIA 1650, ADVIA 1800, and ADVIA 2400 instruments correlate with this panel and demonstrate the linearity of this method in the expected ranges. The data are presented in the table below. Based on the above studies, the limit of detection, and the method comparison study, the sponsor established the assay reportable range for serum and urine at 0.1 – 30 mg/dL and 1 – 245 mg/dL, respectively.

CAP Creatinine LN24A Linearity/Accuracy Panel							
Sample	NIST Assigned Values	ADVIA 1200 ECRE_2 Recovery	% Bias	ADVIA 1650 ECRE_2 Recovery	% Bias	ADVIA 2400 ECRE_2 Recovery	% Bias
LN24-01	0.50	0.50	0.00	0.53	5.00	0.51	1.00
LN24-02	0.74	0.71	-4.05	0.73	-2.03	0.72	-3.38
LN24-03	1.39	1.35	-3.24	1.38	-0.72	1.36	-2.52
LN24-04	2.05	1.97	-3.90	2.03	-1.22	2.00	-2.68
LN24-05	2.71	2.62	-3.51	2.68	-1.29	2.64	-2.58
LN24-06	3.36	3.28	-2.38	3.34	-0.74	3.27	-2.83
LN24-07	4.02	3.94	-1.99	4.00	-0.62	3.93	-2.36

The sponsor also conducted extended linear range studies to establish system parameters that would trigger a re-run (reanalysis) of high serum or urine samples so that the labs can re-test samples without having to perform a manual dilution. The serum and urine samples were tested on all above mentioned ADVIA systems. Based on the sponsors' internal acceptance criteria of ± 10% recovery (neat vs. diluted after reanalysis), the sponsor established the following upper limits of the extended ranges:
ADVIA 1650/1800/2400 serum/plasma: 5 x 30.0 mg/dL = 150 mg/dL
ADVIA 1650/1800/2400 urine: 5 x 245 mg/dL = 1225 mg/dL
ADVIA 1200 serum/plasma: 3 x 30.0 mg/dL = 90 mg/dL
ADVIA 1200 urine: 4 x 245 mg/dL = 980 mg/dL

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

Calibrator. The sponsor uses single point calibration with previously cleared (k030169) Bayer Chemistry Calibrator supplied separately for both serum/plasma and urine. The assigned value of the calibrator is traceable to Isotope Dilution LC Mass Spectrometry reference method, which uses NIST reference material (SRM 967).

Controls. To ensure adequate quality control, the sponsor provides and recommends assaying two quality controls, along with the samples. The control materials have been previously cleared (k883209) and are supplied separately.

d. Detection limit:

The sponsor evaluated Limit of Detection (LoD) and Limit of Blank (LoB) on all ADVIA instruments listed above following the guidelines in CLSI EP17-A. Based on the evaluation of 59 blank (saline) and 58 low-level (control 1 at 1.7 mg/dL) sample values, the LoD was established at 0.1 mg/dL following the algorithm, LoD = mean of blank + (1.6455 X SD of blank) + (1.645 X SD of Low sample).

e. Analytical specificity:

The sponsor evaluated the effect of hemoglobin (0-1000 mg/dL), unconjugated bilirubin (0 – 30 mg/dL), conjugated bilirubin (0-30 mg/dL), and lipemia (intralipid) (0-1000 mg/dL) on normal serum control samples (1 mg/dL and 3 mg/dL) spiked with the interferents, and then compared with unspiked control. Based on the sponsor-defined interference limit of ± 10% of control, the following interference limit claims were set by the sponsor for ADVIA 1200, ADVIA 1650/1800, and ADVIA 2400 instruments tested.

Interference results at 1 mg/dL creatinine

Interferent	No Interference (±10%) claim up to (mg/dL)		
	ADVIA 1200	*ADVIA 1650*	*ADVIA 2400*
Hemoglobin	500	750	500
Lipemia	1000	1000	1000
Unconjugated bilirubin	30	30	30
Conjugated Bilirubin	30	30	30

Interference results at 3 mg/dL creatinine

Interferent	No Interference (±10%) claim up to (mg/dL)		
	ADVIA 1200	*ADVIA 1650*	*ADVIA 2400*
Hemoglobin	1000	1000	1000
Lipemia	1000	1000	1000
Unconjugated bilirubin	30	30	22.5
Conjugated Bilirubin	30	30	30

Using an ADVIA 2400, the sponsor tested the following medications for interference at a creatinine level of 0.8 – 1.1 mg/dL.

Medication	Medication Level (µg/mL)	Interference*
Acetaminophen	200	NSI
Cefoxitin	2230	-11%
Cephalexin	200	NSI
Dipyrone	200	-13%
Dobesilate	400	-79%
Dobutamine	20	-10%
Dopamine	20	-15%
Ethylglycine	6	13%
Fluorocytosine	200	NSI
L-dopa	20	NSI
Methyl dopa	7	NSI

Phenylbutazone	200	NSI
Proline	20	NSI
Salicylate	200	NSI

*NSI = No Significant Interference. A percentage effect ≥ 10% is considered a significant interference.

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:
Performance of the ADVIA Chemistry Enzymatic Creatinine_2 assay was compared with the predicate device, ADVIA Chemistry Systems Creatinine_2 (CREA_2) (k973993). The ADVIA instrument systems 1200, 1650, and 2400 were used for the comparison. A summary of the sample number, composition, and the results of linear regression analysis is given below for serum and urine. The sponsor found correlation between the predicates and the new device for both serum and urine samples on ADVIA systems as follows:

Specimen Type	Predicate/Instrument	n	Regression Equation	R	Sample range (mg/dL)
Serum	CREA_2/ADVIA1200	60	y = 1.017x+0.03	1.00	0.3 – 12.3
Serum	CREA_2/ADVIA1650	60	y = 1.018x-0.04	1.00	0.3 – 11.9
Serum	CREA_2/ADVIA2400	60	y = 1.026x-0.03	1.00	0.3 – 12.1
Urine	CREA_2/ADVIA1200	46	y = 1.042x+0.41	1.00	20.0 – 238.1
Urine	CREA_2/ADVIA1650	49	y = 1.019x-0.99	1.00	17.8 – 239.4
Urine	CREA_2/ADVIA2400	44	y = 1.025x-2.47	0.99	18.9 – 218.1

In another method comparison study, serum samples were tested on all three instruments. The following results were obtained:

Specimen Type	Predicate/Instrument	n	Regression Equation	R	Sample range (mg/dL)
Serum	CREA_2/ADVIA1200	28	y = 1.047x+0.01	1.00	0.5 – 25.6
Serum	CREA_2/ADVIA1650	42	y = 1.059x-0.15	1.00	0.6 – 25.7
Serum	CREA_2/ADVIA2400	42	y = 1.054x-0.14	1.00	0.6 – 25.4

The sponsor also conducted a reference method correlation study using Isotope dilution mass spectrometry (IDMS), as recommended by the National Kidney Disease Education Program (NKDEP). Twenty five serum samples ranging in concentration from 0.5 – 4.5 mg/dL were assayed in three replicates within a day and found to produce the correlation equation (y = 0.981x -0.01; r = 0.999) between the device and the IDMS method.

b. Matrix comparison:

To demonstrate comparable performance between serum and lithium-heparin or potassium-EDTA plasma, the sponsor compared 42 samples on ADVIA instrument systems 1200, 1650, 1800 and 2400. Some samples were spiked with creatinine to extend the sample test range. Compared with the sera for the sample values ranged (0.4 ~ 26 mg/dL), the mean recovery for the lithium-heparin or potassium-EDTA plasma produced the following resuls:

Specimen Type	Predicate/Instrument	n	Regression Equation	R	Sample range (mg/dL)
EDTA	ECRE_2/ADVIA1200	43	y = 1.021x-0.03	0.998	0.4 – 28.2
Heparin	ECRE_2/ADVIA1200	43	y = 1.011x+0.04	0.999	0.4 – 28.6
EDTA	ECRE_2/ADVIA1650	43	y = 1.016x-0.02	0.999	0.3 – 25.6
Heparin	ECRE_2/ADVIA1650	43	y = 1.005x+0.05	0.999	0.4 – 26.0
EDTA	ECRE_2/ADVIA2400	42	y = 1.015x+0.0	0.998	0.4 – 26.8
Heparin	ECRE_2/ADVIA2400	42	y = 1.006x+0.07	0.999	0.4 – 27.3

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):

4. Clinical cut-off:
Not Applicable

5. Expected values/Reference range:
The expected values of creatinine were based on literature*. The sponsor states that they provide these ranges for reference only and each laboratory should establish its own normal range.

Sex	Expected Values for Serum/Plasma	Expected Values for Urine
Males	0.6 – 1.1 mg/dL (53 – 97 µmol/L)	800 – 2000 mg/day (7.1 – 17.7 mmol/day)
Females	0.5 – 0.8 mg/dL (44 – 71 µmol/L)	600 – 1800 mg/day (5.3- 15.9 mmol/day)

* Tietz NW. Clinical Guide to Laboratory Tests. 4th ed. St. Louis, MO: WB Saunders Company; 2006:316.

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.