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

A. 510(k) Number:

k090330

B. Purpose for Submission:

New device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic, quantitative

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Vista Enzymatic Creatinine Flex Reagent Cartridge

Dimension Vista Enzymatic Creatinine Calibrator

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1225 Creatinine Test System

   21 CFR 862.1150 Calibrator

2. Classification:

   Class II

3. Product code:

   JFY and JIT, respectively

4. Panel:

   Clinical Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for use statements below.

2. Indication(s) for use:
   The ECREA method is an *in vitro* diagnostic test for the quantitative measurement of creatinine in human serum, plasma and urine on the Dimension Vista® System. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for other urine analytes.

   The ECREA CAL is an *in vitro* diagnostic product for the calibration of the Enzymatic Creatinine (ECREA) method on the Dimension Vista® System.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Performance characteristics were provided for the Dimension Vista System 1500

I. Device Description:

The Dimension Vista® ECREA Flex® reagent cartridge is a prepackaged *in-vitro* diagnostic test method. The reagents contained in the Dimension Vista® ECREA Flex® reagent cartridge are: Reagent 1 – TAPS buffer, creatinase, sarcosine oxidase, HTIB; Reagent 2 - TAPS buffer, creatininase, horseradish peroxidase, 4-aminophenazone, and potassium hexacyanoferrate (II).

The Dimension Vista® ECREA CAL is an ECREA CAL is a liquid, bovine serum albumin, based product containing creatinine. The kit consists of six vials, three vials per level (A, B), 2.5 mL per vial. The approximate values are 0.95 mg/dL (Cal A) and 20 mg/dL (Cal B).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Creatinine Plus Reagent and Dimension Chem I Cal

2. Predicate K number(s):

   k003261 and k860021, respectively.

3. Comparison with predicate:

	Dimension Vista® ECREA Flex® reagent cartridge	**Creatinine Plus Reagent (k003261)**
Similarities		
Measurement	Bichromatic end point	Bichromatic end point
Sample Type	Plasma, serum, and urine	Plasma, serum and urine
Differences		
Intended Use	The ECREA method is an *in vitro* diagnostic test for the quantitative measurement of creatinine in human serum, plasma, and urine on the Dimension Vista® System. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for other urine analytes.	Enzymatic in vitro assay for the direct quantitative determination of creatinine in human serum, plasma and urine using Roche clinical chemistry analyzers.
Measuring Range	Serum, Plasma - 0.14 -20.0 mg/dL Urine – 2.80 – 400 mg/dL	Serum, Plasma -0.03 – 30 mg/dL Urine – 0.3 – 400 mg/dL
Sample Size	2.7 µL	6 µL

Feature	**ECREA CAL**	**Dimension® Chem I CAL (DC18B) (k860021)**
Similarities		
Matrix	Bovine Albumin	Bovine Albumin
Differences		
Intended Use	The ECREA CAL is an *in vitro* diagnostic product for the calibration of the Enzymatic Creatinine (ECREA) method on the Dimension Vista® System.	The Dimension® Chemistry I Calibrator is an in vitro diagnostic product to be used to calibrate the Dimension® clinical chemistry system for the Calcium (CA), Creatinine (CREA/ECRE), Glucose (GLU/GLUC), Urea Nitrogen (BUN), and Uric Acid (URCA) methods.
Analyte	Creatinine	Calcium, Creatinine, Glucose, Urea

		Nitrogen, Uric Acid
Matrix	Bovine Albumin	Bovine Albumin
Form	Liquid	Lyophilized
Volume	Six vials, three vials per level (A, B), 2.5 mL per vial	Six vials, two vials per level (1, 2, 3), 2.0 mL per vial
Levels	Three levels: 0, 0.95, 20.0 mg/dL.	Three levels: 0.0, 11.1, 22.4 mg/dL

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

Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)

Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A)

Protocols for Determination of Limits of Detection and Limits of Quantitation (EP17-A)

Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A 1995)

Evaluation of the Linearity of Quantitative Measurement (EP6-A)

L. Test Principle:

Creatininase (in the first reagent) hydrolyzes creatinine in a sample to creatine. Creatine is hydrolyzed by creatinase to sarcosine and urea. Sarcosine from this reaction is oxidized by sarcosine oxidase to glycine and formaldehyde and hydrogen peroxide. The hydrogen peroxide reacts with 4-aminoantipyrine and an acid in the presence of peroxidase to yield a quinine imine chromogen. The resulting change in absorbance at 540 and 770 nm is proportional to the creatinine concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision studies for serum and urine samples were evaluated using CLSI EP5-A as a guideline. The sponsor conducted a 20 day ANOVA study with the Dimension Vista 1500 instrument. The sponsor conducted within run precision (repeatability), between run precision, between day precision and within lab precision (total) with two serum pools, two serum controls, two urine pools and two urine controls. For within-run precision, samples were run in singlet for twenty days (n=20). For total precision, samples were tested twice daily, in duplicate over 20 days (n=80). Results of the precision studies

for serum and urine samples are shown below.

		Serum Pool		Serum Control		Urine Pool		Urine Control	
		1	2	1	2	1	2	1	2
Within-run (repeatability)	Mean (mg/dL)	0.61	1.57	0.79	5.81	112.19	282.19	64.10	149.84
	SD (mg/dL)	0.02	0.02	0.02	0.05	1.8	3.51	1.57	2.74
	% CV	2.9	1.4	2.4	0.84	1.63	1.2	2.45	1.83
Between-run	Mean (mg/dL)	0.61	1.57	0.79	5.81	112.19	282.19	64.10	149.84
	SD (mg/dL)	0.01	0.02	0.01	0.09	2.6	6.46	1.74	4.01
	% CV	2.0	1.4	1.9	1.5	2.3	2.29	2.7	2.67
Between-day	Mean (mg/dL)	0.61	1.57	0.79	5.81	112.19	282.19	64.10	149.84
	SD (mg/dL)	0.02	0.02	0.02	0.00	0.00	4.53	1.0	0.94
	% CV	2.7	1.3	2.3	0.00	0.00	1.6	1.55	0.61
Within-lab (total)	Mean (mg/dL)	0.61	1.57	0.79	5.81	112.19	282.19	64.10	149.84
	SD (mg/dL)	0.03	0.04	0.03	0.10	3.15	8.64	2.55	4.94
	% CV	4.4	2.4	3.8	1.7	2.8	3.06	3.97	3.30

b. Linearity/assay reportable range:

Serum and urine linearity were assessed via recovery studies using EP6-A as a guideline. Studies are conducted on the Dimension Vista 1500 instrument

Serum

Serum samples were assayed in replicates of five and linear regression equations were determined. Serum samples were spiked with anhydrous creatinine and nine lower concentrations were prepared using Dimension Vista Calibrator level 1 as a diluent. Serum samples concentrations ranged from 0.0 to 25.46 mg/dL. The serum linear equation is y=0.993x-0.14 and the recoveries ranged from 87.9 to 100%. The linear equation and recovery results and limit of detection (LoD) in d. below support the sponsor's claimed serum linear range of 0.14 to 20 mg/dL.

Urine

Urine samples were assayed in replicates of five and linear regression equations were determined. Urine samples were spiked with anhydrous creatinine directly into urine to make a high sample and nine lower

concentrations were prepared using deionized water as a diluent. Urine concentrations ranged from 0.00 to 464.80 mg/dL. The urine linear equation is y=0.991x-2.96 and the recoveries ranged from 93.7 to 106.9%. The linear equation and recovery results and LoD in d. below support the sponsor's claimed urine linear range of 2.8 to 400 mg/dL.

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

Traceability

The Dimension Vista Enzymatic Creatinine Calibrator is traceable and prepared gravimetrically from the NIST standard reference material SRM914.

Value assignment

Six levels of the in house master calibrators are prepared from the stock solution that is traceability to NIST 914 SRM Creatinine standard reference material. Level 1 does not contain analyte and is assigned a value of 0 mg/dL. The creatinine standards used in these calibrators is prepared using an in-house gravimetric preparation. Standards were tested in replicates of 5 per level assayed with multiple lots on multiple instruments. The sponsors acceptance criteria for the obtained values for calibrator A and B are 0.8 to 1.0 mg/dL and 20 to 22 mg/dL respectively. Working calibrators are traceable to the in-house master calibrators with similar protocols.

Stability

Stability characteristics of the Dimension Vista ECREA Calibrator were determined stressed and accelerated studies. Real-time studies are on-going. Four different stressed conditions were test at five time periods. The results from the studies support the sponsor's claimed shelf-life of 12 months at 4 °C, closed (sealed) stability of 30 days on the instrument and open vial (punctured) stability of 5 days at 2-8° C.

d. Detection limit:

The sponsor assessed the Limit of the Blank (LoB) and Limit of Detection (LoD) according to the CLSI EP17-A guideline. The LoB was determined by assaying five blank samples (deionized water) in replicates of four (n=20) and adding 2 standard deviations of the mean. The LoD was determined by assaying four replicates of 5 samples (with concentrations close to 4 times the LoB) per day for three days. The samples were assayed on four instruments by one operator. The results for LoB are 0.07 mg/dL and for LoD are 0.14 mg/dL for serum. The LoD for urine was calculated to be 2.8 mg/dL.

Analytical specificity:

Interference studies to determine the effects of unconjugated bilirubin, hemolysis and lipemia were performed according to CLSI EP-7A. The sponsor states that interferences are considered to be significant if the bias between the test and control samples are greater than 10%.

Assay performance claims have been established on the Dimension Vista System 1500 by testing a serum pool containing approximately 1.0 mg/dL creatinine to the following concentrations of each interferent:

Unconjugated and conjugated Bilirubin – 30 and 40mg/dL;
Results:
Bilirubin: No significant interference at 30 mg/dL.
Concentrations greater than 30 mg/dL bilirubin may cause interference.

Hemolysis – 500 and 600 mg/dL;
Results:
Hemolysis: No significant interference at 500 mg/dL.
Concentrations greater than 500 mg/dL may cause interference. The sponsor states in the package insert the following "moderately hemolyzed specimens should not be used with the ECREA method".

Lipemia (intralipid) – 1000 and 4000 mg/dL.
Results:
Lipemia (Intralipid): No significant interference at 1000 mg/dL.
Concentrations greater than 1000 mg/dL may cause interference.

The sponsor has the following interference section in the package insert:

Hemoglobin at 600 mg/dL [0.37 mmol/L] decreases ECREA results by 10% at 1.02 mg/dL [90.2 μmol/L] creatinine.

Bilirubin (unconjugated) at 40 mg/dL [707 μmol/L] decreases ECREA results by 19% at 1.01 mg/dL [89.3 μmol/L] creatinine.

Bilirubin (conjugated) at 40 /dL [707 μmol/L] decreases ECREA results by 16% at 1.01 mg/dL [89.3 μmol/L] creatinine.

Lipemia at 3000 mg/dL [33.9 mmol/L] increases ECREA by 25% at 1.01 mg/dL [89.3 μmol/L] creatinine.

In additional, the sponsor has an extensive list of substances tested in the package insert and found no significant interferences.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A comparison study was performed using CLSI EP9-A2 as a guideline with this device and a commercially available enzymatic method.

One-hundred and thirty serum samples that ranged from 0.57 -19.9 mg/dL were assayed in singlicate with the current method using the Dimension Vista 1500 (y-axis) and a creatinine assay using the Hitachi 917 (x-axis). The resulting linear regression equation is y=1.029x-0.177 mg/dL with a correlation coefficient of 1.00.

One-hundred and twenty-six urine samples that ranged from 8.2 to 391 mg/dL were assayed in singlicate with the current method using the Dimension Vista 1500 (y-axis) and a creatinine assay using the Hitachi 917 (x-axis). The resulting linear regression equation is y=1.057x-6.11 mg/dL with a correlation coefficient of 0.999.

The sponsor has conducted a method comparison to a reference procedure called Isotope Dilution-Gas Chromatography/ Mass Spectrometry (ID-GC/MS) to evaluate commutability. Thirty-two serum samples ranging from 0.5 to 40.9 mg/dL were evaluated against the ID-GC/MS method. The resulting linear regression equation was y=1.027x-0.015 with a correlation coefficient of 0.9985. Twenty urine samples ranging from 25.7 to 404.0 mg/dL were also evaluated against the ID- GC/MS method. The resulting linear regression equation was y=1.019x-3.089 with a correlation coefficient of 0.998.

b. Matrix comparison:

Fifty-six matched sets of serum(x)/ lithium heparin plasma (y)/ sodium heparin (y) samples ranging from 0.53 to 17.25 were assayed with the Dimension Vista 1500 using EP9-A2 as a guideline. Sixteen of the fifty-six samples were spiked to obtain higher creatinine concentrations. The following tables show the linear regression results from the comparison of serum to the plasmas tested.

Serum	Li-Heparin	Na-Heparin
Linear Regression Equation	Y=0.9745x + 0.0634	Y=0.978x + 0.0745
Correlation Coefficient	0.9981	0.9965

The sponsor concluded that lithium heparin and sodium heparin are acceptable

anticoagulants.

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:

   The sponsor references literature for the expected values as follows:
   Expected Values:

   Serum/plasma[1]
   Males: 0.67 – 1.17 mg/dL [59.2 – 104 μmol/L]
   Females: 0.51 – 0.95 mg/dL [45.1 – 84 μmol/L]

   Random Urine[1]
   Males: 40.0 – 278 mg/dL [3.54 – 24.6 mmol/L]
   Females: 29.0 – 226 mg/dL [2.56 – 20.0 mmol/L]

   24-Hour Urine Excretion[2]
   Males: 0.87 – 2.41 g/day [51.2– 142 mmol/day]
   Females: 0.67 – 1.59 g/day [5.92 – 141 mmol/day]

   [1] Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studyies for enzymatic and Jaffe creatinine assays in plasma and serum and early morning urine. Clin. Lab. 2000; 46:53-55.

   [2] Junge W, Wilke B, Halabi A., et al. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. Clin Chim Acta 2004; 344; 137-148.

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.