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

A. 510(k) Number:

k132638

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:
Dimension® Creatinine (CRE2) Flex® reagent cartridge

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CGX	Class II	Creatinine test system (21CFR 862.1225)	75-Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:
   The CRE2 method is an in vitro diagnostic test for the quantitative measurement of creatinine in human serum, plasma, and urine on the Dimension® clinical chemistry system. Creatinine measurements are used in the diagnosis and treatment of certain renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

3. Special conditions for use statement(s):
   Not applicable

4. Special instrument requirements:
   Dimension® EXL 200 clinical chemistry system

I. Device Description:

Dimension® Creatinine (CRE2) Flex® reagent cartridge includes two major reagents. Reagent 1 consists of 125 mM Lithium Picrate and reagent 2 consists of 2000 mM Sodium Hydroxide with 2.7 mM potassium ferricyanide.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Dimension® clinical chemistry system Creatinine (CREA) Flex® reagent cartridge

2. Predicate 510(k) number(s):
   k925668

3. Comparison with predicate:

Similarities

	Dimension® Creatinine (CRE2) Flex® reagent cartridge (Candidate device)	Dimension® clinical chemistry system Creatinine (CREA) Flex® reagent cartridge (Predicate Device) k925668
Intended Use	The CRE2 method is an in vitro diagnostic test for the quantitative measurement of creatinine in human serum, plasma, and urine on the Dimension® clinical chemistry system. Creatinine measurements are used in the diagnosis and treatment of certain renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.	Same

Device Technology (detection)	Modified Jaffe Methodology (creatinine alkaline picrate) with photometric detection	Same
Detection Conditions	Wavelength = 510 and 600 nm Type of Measurement = Bichromatic rate	Same
Sample Volume	20 µL	Same
Reagents	Reagent 1 = Lithium Picrate (125 mM) Reagent 2 = Sodium Hydroxide (2000 mM) with potassium ferricyanide (2.7	Same
Reagent Volumes	Volume of Reagent 1 used = 74 µL Volume of Reagent 2 used = 18 µL Volume of Diluent used = 258 µL	Same
Calibration Interval	90 days - same reagent lot	Same
Limit of Blank/Analytical Sensitivity	Limit of Blank: 0.05 mg/dL	Analytical Sensitivity : 0.05 mg/dL
Calibration	Chem 1 Calibrator (DC18C) 3 levels (n=3)	Same

Differences

	Dimension® Creatinine (CRE2) Flex® reagent cartridge (Candidate device)	Dimension® clinical chemistry system Creatinine (CREA) Flex® reagent cartridge (Predicate Device) k925668
Measuring Range (serum)	0.15 - 20.00 mg/dL	0 – 20.0 mg/dL
Measuring Range (urine)	5.00 – 400.00 mg/dL	0 – 200.0 mg/dL
Expected Values	Serum and Plasma Males: 0.70 – 1.30 mg/dL Females: 0.55 – 1.02 mg/dL Urine Males: 0.95 – 2.49 g/24 hr Females: 0.60 – 1.80 g/24 hr	Serum Males: 0.8 – 1.3 mg/dL Females: 0.6 – 1.0 mg/ Urine Males: 0.6 – 2.5 g/24 hr Females: 0.6 – 1.5 g/24 hr
Interferences	No significant interference at a Creatinine concentration of 1.5 mg/dL from: Hemoglobin at 500 mg/dL Bilirubin (conjugated) at 20 mg/dL, Bilirubin (unconjugated) at 10 mg/dL Lipemia (Intralipid) at 1000 mg/dL.	No significant interference at a Creatinine concentration of 1.7 mg/dL from: Hemoglobin at 1000 mg/dL, Bilirubin (unconjugated) at 5 mg/dL Lipemia (Intralipid) at 200 mg/dL

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

- CEN 13640: Stability Testing of In Vitro Diagnostic Reagents
- CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline
- CLSI EP09-A2-IR Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline
- CLSI EP05-A2: Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline
- CLSI EP-06-A: Evaluation of the Linearity of Quantitative Measurement
- CLSI EP17-A2: Protocols for Determination of Limits of Detection and Limits of Quantitation
- CLSI C28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline- Third Edition

L. Test Principle:

Dimension® Creatinine (CRE2) Flex® reagent cartridge is used to measure the creatinine concentration in human serum, plasma, and urine on the Dimension® clinical chemistry system using quantitative, photometric/colorimetric methods . The CRE2 method uses a modified kinetic Jaffe technique to measure the creatinine concentration. In the presence of a strong base such as sodium hydroxide, picrate reacts with creatinine to form a red chromophore. The system monitors rate of increasing absorbance at 510 nm due to the formation of this chromophore is directly proportional to the creatinine concentration in the sample and is measured using a bichromatic (510, 600nm) rate technique. Bilirubin is oxidized by potassium ferricyanide to prevent interference.

M. Performance Characteristics (if/when applicable):

The following data represent typical method performance. These data were collected on the Dimension EXL 200 integrated chemistry system.

1. Analytical performance:

   a. Precision/Reproducibility:
   Within-run (repeatability) and total imprecision (Intermediate precision) studies for the Dimension® Creatinine (CRE2) Flex® reagent cartridge were designed from CLSI Guideline EP5- A2, "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition."

   The precision/repeatability study was performed using two (2) serum pools, three (3) levels of BioRad Multiqual serum material, two (levels) of BioRad Liquicheck urine material and two (2) urine pool.

   The samples were tested on Dimension® clinical chemistry system using five different creatinine concentrations 0.71, 1.32, 1.79, 7.04 and 15.79 mg/dL, respectively. The urine was tested with four different creatinine concentrations 39.31,

62.28, 142.80 and 339.56 mg/dL, respectively. For intermediate precision, testing was performed over twenty (20) days, two (2) separate runs with two test samples for each test material. The results are summarized below:

			Repeatability		Within-Lab	
Sample		Mean (mg/dL)	SD	%CV	SD	%CV
Serum	Serum Pool 1	1.32	0.04	3.0	0.04	3.2
	Serum Pool 2	15.79	0.19	1.2	0.19	1.2
	BioRad Multiqual Level 1	0.71	0.03	4.7	0.04	5.1
	BioRad Multiqual Level 2	1.79	0.04	2.1	0.05	2.8
	BioRad Multiqual Level 3	7.04	0.07	1.0	0.09	1.3
Urine	Urine Pool 1	39.31	1.52	3.9	1.53	3.9
	Urine Pool 2	339.56	4.28	1.3	4.59	1.4
	BioRad Liquicheck Level 1	62.28	0.61	1.0	1.41	2.3
	BioRad Liquicheck Level 2	142.80	1.56	1.1	3.39	2.4

b. Linearity/assay reportable range:

1) Serum samples

Samples were prepared by using serum spiked with creatinine stock at mean concentrations of 0, 0.34, 0.69, 1.38, 2.75, 5.50, 8.25, 11.00, 13.75, 16.50, 19.25, 22 mg/ dL in serum for Dimension® clinical chemistry system. At each creatinine level, 5 replicates were tested. Values from the 12 levels were compared with previously established target values. The results from regression analysis are summarized below:

$Y = 1.0063x + 0.1027$, $R^2=0.9999$

The results of the linearity study support the claimed measuring range of 0.15 - 20.00 mg/dL for creatinine in Dimension® Creatinine (CRE2) Flex® reagent cartridge

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2) Urine samples

The samples were prepared by urine spiked with glucose stock at mean concentrations of and 2.61, 9.22, 15.82, 29.03, 55.45, 108.29, 161.13, 213.98, 266.82, 319.66, 372.50, 425.34 mg/ dL in urine for Dimension® clinical chemistry system. At each creatinine level, 5 replicates were tested. Values from

the 12 levels were compared with previously established target values. The results from regression analysis are summarized below:

$Y = 0.9983x + 0.4103$, $R^2=0.9999$

The results of the linearity study support the claimed measuring range of 5-400 mg/dL for creatinine in Dimension® Creatinine (CRE2) Flex® reagent cartridge

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

Traceability, stability and value assignment –

Traceability and value assignment: The values assigned to Dimension CHEM1 calibrator for creatinine are traceable to NIST SRM 914a. NIST SRM914a is an Isotope Dilution-Liquid Chromatography/ Mass Spectrometry (IDMS) traceable standard. The commutability of the creatinine working standards is verified using recovery of NIST SRM 967, an IDMS traceable, commutable, and frozen serum creatinine reference material. Dimension Instruments are calibrated with the working standards and used to assign the product calibrators via the standard value assignment process. The CHEM I calibrator described in the Dimension Creatinine (CRE2) labeling was previously cleared. The 510(k) number for this product is K860021.

A Flex® cartridge open well stability study was conducted to ensure the reagents perform consistently throughout the claimed open well stability which is 3 days. The protocol and acceptance criteria were found adequate.

d. *Detection limit:*
The Limit of Blank, Limit of Detection and Limit of Quantitation of Dimension® Creatinine (CRE2) Flex® reagent cartridge were determined according to CLSI EP17-A2 in the following manner:

LoB = Mean of Blank Measurement + 1.645 x Standard Deviation of Blank Measurements

LoD = Limit of Blank + CpSDs

- Cp is a correction factor for the 95% CI normal variate to account for bias in the SDS estimate.
- SDS is an estimate of method imprecision pooled from replicates of the low analyte samples

The Limit of Quantitation (LoQ) for the Dimension® Creatinine (CRE2) Flex® reagent cartridge for serum and plasma is 0.15 mg/dL and based on allowable total error of 0.15 mg/dL, determined consistent with CLSI Guideline EP17-A2.

Based upon the results, the results are as follows:

Dimension® CRE2 Limit of Detection Results with Serum		
Limit	Protocol	Value
LoB	4 samples with no analyte were tested (N=5) for 3 days, one run per day, 2 reagent lots,	0.05 mg/dL
LoD	4 low patient serum samples were tested (N=5) for 3 days, one run per day, 2 reagent lots	0.1 mg/dL
LoQ	LoQ was determined by evaluating 4 low level samples with multiple replicates over 3 days multiple measurements per sample. Sponsor defined LoQ as concentration with 20% CV inter-precision at the 95% confidence limit.	0.15 mg/dL

Dimension® CRE2 Limit of Detection Results with Urine		
Limit	Protocol	Value
LoB	4 samples with no analyte were tested (N=5) for 3 days, one run per day, 2 reagent lots,	1.00 mg/dL
LoD	4 low patient urine samples were tested (N=5) for 3 days, one run per day, 2 reagent lots	2.00 mg/dL
LoQ	LoQ was determined by evaluating 4 low level samples with multiple replicates over 3 days multiple measurements per sample. Sponsor defined LoQ as concentration with 20% CV inter-precision at the 95% confidence limit.	5.00 mg/dL

The claimed measuring range is 0.15 - 20.00 and 5 – 400 mg/dL for serum and urine creatinine in Dimension® Creatinine (CRE2) Flex® reagent cartridge respectively based on LoQ and linearity.

See linearity study in M.1.b of this 510(k) decision summary.

e. *Analytical specificity:*
Interference studies were performed for the creatinine measurement function by evaluating potential interfering substances spiked into serum and urine pools at two different creatinine levels, 1.5 and 5.0 mg/dL for serum/plasma, 40 to 175 mg/dL for urine. CLSI EP7A2 was followed for the interference testing. Substances were spiked into serum and urine pool to assess common or known substances which could interfere with the Dimension® Creatinine (CRE2) Flex® reagent cartridge. The sponsor defines interference as bias exceeding 10%. The following substances produced less than 10% deviation when tested on Dimension® Creatinine (CRE2) Flex® reagent cartridge at levels equal to the concentrations listed below.

Serum/Plasma

Substance	Concentration of Substance (mg/dL)
Acetaminophen	20
Acetoacetate	20
Amikacin	8
Ampicillin	5.3
Ascorbic Acid	6
Caffeine	6
Carbamazepine	3
Cephalexin	25
Cephapirin	25
Cephradine	25
Chloramphenicol	5
Chlordiazepoxide	1
Chlorpromazine	0.2
Cholesterol Supertrate	503
Cimetidine	2
Dextran 40	6000
Diazepam	0.51
Digoxin	6.1ng/mL
EDTA	200
Erythromycin	6
Ethanol	400
Ethosuximide	25
Furosemide	6
Gentamicin	1
[illegible]	[illegible]

Ibuprofen	50
Immunoglobulin G (IgG)	5000
Isopropanol	1.0 g/dL
Lidocaine	1.2
Lithium	2.2
Nicotine	0.1
Nortriptyline	1000 ng/mL
Penicillin G (1654	25 U/mL
Pentobarbital	8
Phenobarbital	10
Phenytoin	5
Potassium oxalate	500 mg/dL
Primidone	4
Propoxyphene	0.16
Protein, Albumin	6000
Protein, Total	12g/dL
Salicylic acid	60
Sodium fluoride	400
Theophylline	4
Urea	500
Uric acid	20
Valproic acid	50
Vancomycin	10

Urine

Substance	Concentration of Substance (mg/dL)
50% Acetic Acid	25mL/24 hr collection
6N Hydrochloric Acid	0.6%
6N Nitric Acid	0.6%
Acetone	100 mg/dL
Bilirubin (conjugated)	2 mg/dL
Boric Acid	1% w/v
Ethanol	1 g/dL
Gamma Globulin	0.5 g/dL
Glucose	2 g/dL
Hemoglobin	115 mg/dL
Human Serum Albumin	0.5 g/dL
Oxalic Acid	0.1 g/dL
Sodium Carbonate	5g/24 hr collection
Sodium Fluoride	1% w/v

The following substances had no significant interference (less than 10% interference) when tested on Dimension® Creatinine (CRE2) Flex® reagent cartridge at the concentrations listed below.

Serum/plasma

Substance	Concentration of Substance
Acetone	9.375 mg/dL
Bilirubin (unconj)	10 mg/dL
Bilirubin (conjugated)	20 mg/dL
Cefoxitin	3.75 mg/dL
Cephalothin	10.0 mg/dL
Glucose	400 mg/dL
Intralipid 20%	1000 mg/dL
Pyruvate	5.26 mg/dL
Triglycerides	2500 mg/dL

Urine

Substance	Concentration of Substance
Ascorbic Acid	0.10 g/dL

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
A total of 191 serum, and 113 urine samples were tested with the Dimension CREA assay cleared under K925668 (Method X) and the candidate Dimension® Creatinine (CRE2) Flex® reagent cartridge (Method Y)

The results across the full assay range were analyzed by linear regression.
Serum and urine samples were analyzed in singlicate and samples tested ranged from 0.4-19.8 mg/dL and 13.5-372.7 mg/dL respectively.

Comparative Method	Range (mg/dL)	Slope	Intercept (mg/dL)	Correlation Coefficient	n	Sample type
Dimension CREA Assay	0.4 – 19.8	1.00	-0.08	0.999	191	serum
Dimension CREA Assay	13.5 – 372.7	1.04	-3.58	0.996	113	urine

b. Matrix comparison:

Fifty six (56) serum and lithium heparin plasma samples were tested on the Dimension® Creatinine (CRE2) Flex® reagent cartridge. One replicate of each sample was processed. All samples in the study were fresh and never frozen. The eight spiked sample sets were prepared by spiking equal amounts of purified creatinine into the matched serum and lithium heparin plasma samples. The samples ranged from 0.5-17.35 mg/dL

The following table summarizes the matrix comparaison studies:

Serum vs.	Slope	Intercept	Correlation Coefficient (r)	Range	n
Lithium Heparin Plasma	1.05	-0.02	0.998	0.50 – 17.35	56

The study demonstrated that serum and is equivalent to lithium heparin plasma for the Dimension CRE2 assay.

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:

Serum/Plasma

Transference defined in CLSI C28-A3c was used to validate established reference ranges for serum and plasma creatinine following CLSI C28-A3c. Serum samples from forty normal healthy adult female donors and forty-three normal healthy adult male donors were tested N=1 using the Dimension CRE2 assay. The range was considered validated if ⩽10% of the samples fell outside of established range.

	Males	Females
Reference Range	0.70-1.30 g/day	0.55-1.02 g/day
N	43	40
Outside Range #	2	1
% Outside Range	4.7%	2.5%

These data support the published ranges for Males (0.7 to 1.3 mg/dL (Tietz 1999) and Females (0.55 to 1.02 mg/dL (Clin Chem 54:3 (2008)).

Urine

Published reference ranges were validated for urine specimens using samples from twenty normal healthy adult female donors and twenty-two normal healthy adult male donors following CLSI C28-A3c. Samples were processed N=1 using the Dimension CRE2 assay. The range was considered validated if ⩽10% of the samples fell outside of established range.

	Males	Females
Reference Range	0.95-2.49 g/day	0.6-1.80 g/day
N	22	20
Outside Range #	2	1
% Outside Range	9.10%	5.00%

The above data support the published ranges for Males (0.95 to 2.49 g/day (Clin Chem Acta 344 (2004) 137-148) and Females (0.6 to 1.8 g/day (Tietz 1999)).

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.