

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

A. 510(k) Number:

k091742

B. Purpose for Submission:

New Device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic, quantitative

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

SYNCHRON Systems Enzymatic Creatinine (CR-E) Reagent

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1225 Creatinine Test Systems

2. Classification:

II

3. Product code:

JFY

4. Panel:

Clinical Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use statements below.

2. Indication(s) for use:

CR-E reagent, when used in conjunction with SYNCHRON Systems, UniCel Systems, and SYNCHRON Systems AQUA CAL 1 and 2 and SYNCHRON CX Calibrator Level 1 and 2, is intended for the quantitative measurement of creatinine (CRE) concentration in human serum, plasma or urine (urine is not available on the SYNCHRON CX PRO Systems).

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.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

UniCel DxC 800 System and SYNCHRON CX7 PRO System

I. Device Description:

SYNCHRON Systems Enzymatic Creatinine (CR-E) Reagent is a prepackaged in two reagent cartridges. The reagents contained in the reagent cartridge are: Creatine amidinohydrolase, sarcosine oxidase, N-thyl-N-(3-sulfopropyl)-3-methylaniline, peroxidase, and 4-aminoantipyrine.

J. Substantial Equivalence Information:

1. Predicate device name(s):

SYNCHRON Systems Creatinine (CR-S) Reagent

2. Predicate K number(s):

k071283.

3. Comparison with predicate:

Item	SYNCHRON Systems Enzymatic Creatinine (CR-E) Reagent- Candidate device	SYNCHRON Systems Creatinine (CR-S) Reagent – Predicate device (k071283)
Similarities and Difference		
Intended Use	CR-E reagent, when used in conjunction with SYNCHRON Systems, UniCel DxC Systems, and SYNCHRON Systems AQUA CAL 1 and 2 and SYNCHRON CX Calibrator Level 1 and 2, is intended for the quantitative measurement of creatinine (CRE) concentration in human serum, plasma or urine (urine is not available on the SYNCHRON CX PRO Systems). 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.	CREA reagent, when used in conjunction with UniCel DxC 600/800 Systems and SYNCHRON Systems Multi Calibrator, is intended for the quantitative determination of creatinine concentration in human serum, plasma or urine. 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.
Methodology	Enzymatic method	Modified rate Jaffe method
Sample Type	Plasma, serum, and urine	Same
Measuring Range	Serum, Plasma: 0.20 -25.0 mg/dL Urine: 10 – 400 mg/dL	Serum, Plasma: 0.30 – 25.0 mg/dL Urine: 10 – 400 mg/dL
Sample Size	10 µL for all sample types	20 µL for serum and plasma, 3 µL for urine

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

Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)

Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)

Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)

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

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

How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline, Second edition (C28-A2)

L. Test Principle:

Creatinine amidohydrolase hydrolyzes creatinine in a sample to creatine. Creatine is hydrolyzed by Creatinine amidohydrolase 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 quinoneimine chromogen. The resulting change in absorbance at 560 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-A2 as a guideline. The sponsor conducted within run precision and total precision with one human serum pool, three serum controls and two urine controls. All samples were tested twice daily, in duplicate over 20 days (n=80). Results of the precision studies are shown below.

Table 1: Precision study results on SYNCHRON CX7 PRO System (for serum sample only)

Material	Mean mg/dL	Within-run SD	Within-run %CV	Total imprecision SD	Total imprecision %CV
Serum control level 1	0.62	0.01	1.4	0.01	1.5
Serum control level 2	4.16	0.02	0.5	0.02	0.6
Serum control level 3	7.69	0.02	0.3	0.04	0.5
Serum pool	1.50	0.02	1.0	0.02	1.0

Table 2: Precision study results on UniCel DxC 800 System (for serum and urine samples)

Material	Mean mg/dL	Within-run SD	Within-run %CV	Total imprecision SD	Total imprecision %CV
Serum control level 1	0.64	0.01	2.1	0.02	2.5
Serum control level 2	4.09	0.01	0.3	0.03	0.7
Serum control level 3	7.56	0.03	0.3	0.06	0.8
Serum pool	1.50	0.01	0.7	0.01	0.9
Urine control level 1	66.45	0.31	0.5	0.68	1.0
Urine control level 2	146.61	0.60	0.4	1.47	1.0

b. Linearity/assay reportable range:

Serum and urine linearity studies were designed based on EP6-A guideline.

Serum

Serum pool samples were used for the linearity study. A low creatinine level serum pool was prepared by diluting an aliquot of the serum pool with saline to achieve the target low concentration. A high creatinine level serum pool was prepared by spiking an aliquot of the serum pool with a spiking solution to achieve the target high concentration. Inter-dilutions of the low and high serum pools were used to prepare seven level of serum for the linearity study. All serum samples were tested in replicates of three on SYNCHRON CX7 PRO system and UniCel DxC 800 system. The recovered creatinine values were plotted against the expected values and an appropriate line fitted by standard linear regression.

Serum samples concentrations tested ranged from 0.15 to 31.16 mg/dL and the serum linear equation is $y = 0.9984x - 0.0636$ for SYNCHRON CX7 PRO system. Serum samples concentrations tested ranged from 0.14 to 31.06 mg/dL and the serum linear equation is $y = 1.0013x - 0.0445$ for UniCel DxC 800 system.

The enzymatic creatinine assay has a serum linearity range of 0.20 to 25.0 mg/dL.

Urine

Urine pool samples were prepared by following the same procedures as described above for serum linearity samples. Urine samples concentrations tested ranged from 3.0 to 500 mg/dL. The urine linear equation is $y = 1.0045x - 1.758$ for UniCel DxC 800 system.

The enzymatic creatinine assay has a urine linearity range of 10 to 400 mg/dL.

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

The SYNCHRON CX systems utilize a two-level calibrator, the SYNCHRON CX calibrator, for the candidate enzymatic creatinine (CR-E) assay. The SYNCHRON CX calibrator has been previously cleared in k942676.

The SYNCHRON LX and UniCel DxC systems utilize a two-level calibrator, the Beckman Coulter AQUA calibrator, for the candidate enzymatic creatinine (CR-E) assay. The Beckman Coulter AQUA calibrator has been previously cleared in k965240.

Both calibrators are traceable to the NIST 912a SRM Creatinine standard reference material. The set point values for creatinine were established by human sample correlation to isotope dilution mass spectroscopy.

The CR-E reagent has a shelf-life stability of 18 months when stored at 2-8°C and an open-vial stability of 30 days when stored at 2-8°C.

d. Detection limit:

The sponsor determined the Limit of Detection (LoD) according to the CLSI EP 17-A guideline. The LoD was determined by assaying one blank sample (saline) and one low sample (with concentrations close to 4 times the LoB) in replicates of twenty. The serum samples were assayed on both SYNCHRON CX 7 PRO system and the UniCel DxC 800 system. The urine samples were assayed on the UniCel DxC 800 system. The sponsor concluded that the LoD for serum is 0.02 mg/dL and for urine is 10.0 mg/dL.

The enzymatic creatinine assay has a serum linearity range of 0.20 to 25.0 mg/dL and urine linearity range of 10 to 500 mg/dL.

e. Analytical specificity:

Interference studies were designed according to CLSI EP7-A2 guideline. Three sample pools which represent low, mid, and high creatinine levels were tested at different levels of the potential interferants. The sponsor states that

interferences are considered to be non-significant if the bias between the test and control samples are within $\pm 6\%$ or ± 0.2 mg/dL.

Results of the interferences studies on SYNCHRON CX 7 PRO and UniCel DxC 800 systems are shown below:

Acetoacetate: Not-significant up to 500 mg/dL tested
Lipemia (intralipid): Not-significant up to 500 mg/dL tested
Lipemia (Serum index): Not-significant up to 8 tested
Ascorbic acid: Not-significant up to 20 mg/dL tested
Glucose: Not-significant up to 2000 mg/dL tested
Bilirubin (unconjugated): Not-significant up to 30 mg/dL tested
Bilirubin (conjugated): Not-significant up to 15 mg/dL tested
Hemoglobin: Not-significant up to 500 mg/dL tested
Dopamine: Not-significant up to 15 $\mu\text{mol/L}$ tested

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A comparison study was performed between the enzymatic creatinine assay (candidate method) and the CRE-S assay (predicate method) according to the CLSI EP9-A2 guideline.

Eighty serum samples that ranged from 0.55- 24.0 mg/dL were assayed on the SYNCHRON CX 7 PRO system and the UniCel DxC 800 system. Some samples are spiked in order to cover the hard-to-find range. The resulting linear regression equation is $y = 0.997x - 0.002$ with a correlation coefficient of 1.00, N= 78, for the SYNCHRON CX 7 PRO system and $y = 0.991x + 0.012$ with a correlation coefficient of 1.00, N=80, for the UniCel DxC 800 system. Y= candidate method and X= predicate method.

Sixty six urine samples that ranged from 12 to 382 mg/dL were assayed on the UniCel DxC 800 system. Some samples are spiked in order to cover the hard-to-find range. The resulting linear regression equation is $y = 0.988x - 3.096$ with a correlation coefficient of 0.998. Y= candidate method and X= predicate method.

b. Matrix comparison:

Fifty-two paired serum and plasma samples (sodium heparin and lithium

heparin) ranging from 0.5 to 25 mg/dL were run with both SYNCHRON CX 7 PRO system and UniCel DxC 800 system. The following tables show the linear regression results from the comparison of serum to the plasma tested.

Serum	Li-Heparin	Na-Heparin
Linear Regression Equation from SYNCHRON CX 7 PRO	$Y=0.995X + 0.005$	$Y=0.999X - 0.006$
Linear Regression Equation from UniCel DxC 800	$Y=0.997X - 0.005$	$Y=1.001X - 0.003$

The sponsor concluded that lithium heparin and sodium heparin are acceptable anticoagulants for samples.

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 serum reference range that the sponsor claimed was based on the predicate device and the transferability of the reference range based on the comparability of the analytical systems according to the CLSI C28-A2 guideline. A reference range confirmation study was performed using 20 subjects (male and female) and 95% of the results fell within the predicate's reference range.

In the labeling, the sponsor's serum reference ranges are:

For SYNCHRON CX PRO system: 0.42-1.09 mg/dL (female), 0.62-1.28 mg/dL (male)

For UniCel DxC 800 system: 0.44-1.00 mg/dL (female), 0.61-1.24 mg/dL (male)

In the labeling, the urine reference range on the UniCel DxC 800 system is based on literature* as follows: 800-2000 mg/24 hours (male), 600-1800 mg/24 hours (female)

* Wu, A., ed. *Tietz Clinical Guide to Laboratory Tests* 4th Edition, Saunders Elsevier, St. Louis, MO 2006.

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.