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

A. 510(k) Number:

k073634

B. Purpose for Submission:

New Device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic, quantitative

E. Applicant:

Sentinel CH. SpA

F. Proprietary and Established Names:

MULTIGENT Creatinine (Enzymatic) Assay

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JFY	Class II	21 CFR§ 862.1225 Creatinine test system	75 - Clinical Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The MULTIGENT Creatinine (Enzymatic) assay is a device intended to measure

creatinine levels in human serum, plasma, and urine using the ARCHITECT c8000 System and the AEROSET System. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a component of various calculations for determination or estimation of creatinine clearance, glomerular filtration rate (GFR) or estimated GFR (eGFR).

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Abbot ARCHITECT c8000 and AEROSET systems

I. Device Description:

The MULTIGENT Creatinine (Enzymatic) Assay is a dual reagent kit. Reagent one contains Good's buffer, creatinase, sarcosine oxidase, ascorbate oxidase, catalase and ESPMT (N-ethyl-N-sulfopropyl-M-toluidine). Reagent 2 contains Good's buffer, creatininase, peroxidase and 4-Aminoantipyrine.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Creatinine Plus Assay

2. Predicate K number(s):

   k003261

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Form	Liquid, ready to use	Same
Test Method	Enzymatic colorimetry	Same
Sample	Serum, plasma, urine	Same

Differences		
Item	Device	Predicate
Measuring Range	Serum: 0.10-40 mg/dl Plasma: 0.10-40 mg.dl Urine: 2.5-400 mg/dl	Serum:0.03-30 mg/dl Plasma: 0.03-30 mg/dl Urine: 0.3-400 mg/dl
Instruments	Abbott Aeroset and Architect systems	Roche Hitachi 911 system

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

CLSI EP5-A, CLSI EP-6A, CLSI EP17A, and CLSI EP9-A2

L. Test Principle:

Creatininase (in reagent 1) 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 ESPMT in the presence of peroxidase to yield a quinoneimine dye. The resulting change in absorbance at 548 nm is proportional to the creatinine concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

i.) Precision studies for serum samples were evaluated using CLSI EP5-A as a guideline. For within-run (intra-assay) and total precision studies, testing was performed on both Architect c8000 and Aeroset systems. For within-run precision, 3 serum controls were run in singlet for one day. For total precision, 3 serum controls were tested twice daily, in duplicate, for over 20 days. Results of the precision studies were shown below:

MULTIGENT Creatinine (Enzymatic) ARCHITECT Serum Precision				
Intra-Assay Precision				
Control		**Level 1**	**Level 2**	**Level 3**
N		20	20	20
Mean (mg/dL)		0.623	0.958	3.752
Intra-assay	SD	0.0055	0.0052	0.0089
	%CV	0.88	0.55	0.24
Total Precision				
N		80	80	80
Mean (mg/dL)		0.654	1.827	6.604
Within Run	SD	0.0042	0.0061	0.0199
	%CV	0.64	0.33	0.30
Between Day	SD	0.0173	0.0265	0.0300
	%CV	2.65	1.45	0.45
Between Run	SD	0.0100	0.0173	0.0520

	%CV	1.53	0.95	0.79
Total	SD	0.0207	0.0314	0.0630
	%CV	3.17	1.72	0.95

MULTIGENT Creatinine (Enzymatic) AEROSET Serum Precision				
Intra-Assay Precision				
Control		**Level 1**	**Level 2**	**Level 3**
N		20	20	20
Mean (mg/dL)		0.624	0.973	3.746
Intra-assay	SD	0.0059	0.0080	0.0190
	%CV	0.94	0.82	0.51
Total Precision				
N		80	80	80
Mean (mg/dL)		0.647	1.826	6.606
Within Run	SD	0.0077	0.0077	0.0165
	%CV	1.19	0.42	0.25
Between Day	SD	0.0100	0.0224	0.0374
	%CV	1.55	1.23	0.57
Between Run	SD	0.0000	0.0000	0.0245
	%CV	0.00	0.00	0.37
Total	SD	0.0126	0.0237	0.0475
	%CV	1.95	1.30	0.72

ii.) Precision studies for urine samples were evaluated according to the CLSI EP5-A guideline. For total precision studies, two urine controls were tested twice daily, in duplicate, for over 20 days and were assayed on both the Architect c8000 and the Aeroset system. Urine controls were diluted x 10 with 0.9% saline before testing. Results of the total precision studies were shown below:

MULTIGENT Creatinine (Enzymatic) ARCHITECT Urine Precision Total precision Data Summary		
Control	**Level 1**	**Level 2**
N	80	80
Mean (mg/dL)	69.940	124.724

Within Run	SD	0.6324	1.1068
	%CV	0.90	0.89
Between Day	SD	0.5782	0.4243
	%CV	0.83	0.34
Between Run	SD	0.5505	0.8358
	%CV	0.79	0.67
Total	SD	1.0184	1.4504
	%CV	1.46	1.16

MULTIGENT Creatinine (Enzymatic) AEROSET Urine Precision Total precision Data Summary			
Control		**Level 1**	**Level 2**
N		80	80
Mean (mg/dL)		68.769	121.937
Within Run	SD	0.8699	1.4059
	%CV	1.26	1.15
Between Day	SD	0.3317	0.2387
	%CV	0.48	0.20
Between Run	SD	0.4136	0.5834
	%CV	0.60	0.48
Total	SD	0.9023	1.5033
	%CV	1.31	1.23

b. Linearity/assay reportable range:

Linearity study was assessed according to CLSI EP-6A.

i.) Serum samples: Serum linearity was assessed on three different ranges of human sera: whole analytical measuring range (2.3 to 53 mg/dL), pathologic analytical measuring range (pre dialysis range of 0.39 to 9.7 mg/dL) and low analytical measuring range (0.04 to 2.2 mg/dL). The spiked pools were serially diluted to obtain a set of at least 10 samples with proportionally decreased concentrations of creatinine. Serum sample pools were assayed in triplicates. The sponsor's acceptance criterion was a bias of 5% between the expected values and the observed values. The study supported the sponsor's linearity claim range of 0.1 to 40.0 mg/dL.

ii.) Urine samples: Urine linearity was assessed on a pool of human urine that was spiked with a concentrated solution to obtain a final analyte concentration exceeding the targeted high linearity and was serially diluted to obtain a set of at least 12 samples with proportionally decreased concentrations of creatinine. The study covered the entire analytical measuring range (22.9 to 476.6 mg/dL) and the low analytical measuring range (2.39 to 52.45 mg/dL).Urine sample pools were run in triplicates and the sponsor's acceptance criterion was a bias of 5% between the expected values and the observed values. The study supported the sponsor's linearity claim range of 2.5 to 400 mg/dL.

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

The assay is traceable to IDMS values through SRM967.

This device does not include the calibrator materials. The sponsor's labeling recommends using the MULTIGENT Clin Chem Calibrators (cleared in k070971). The sponsor states that the recommended calibrators are stable for 60 days when stored on-board and is required for each new lot of reagent.

The sponsor conducted open on-board, closed stability (reagent) and calibration stability of reagents 1 and 2 on both the ARCHITECT c8000 and AEROSET systems. On-board stability of the assay reagents was conducted with new calibrators, two control materials and a prepared human serum sample and calibrator were analyzed over 98 days- every 3 to 4 days. Shelf-life stability was determined using an accelerated stability study. The sponsor's on-board/open stability for the MULTIGENT Creatinine (Enzymatic) Assay reagents is stable up to 60 days at 2-10° C and has a shelf life stability of 120 days when stored at 2-8° C.

d. Detection limit:

i.) A detection limits study was performed according to the CLSI EP17A guideline for the serum samples. The serum LOB was determined by assaying saline and human control serum in replicates of 20 for 3 different runs on the Aeroset and Architect instruments. The serum LOD was determined by assaying a human control serum mixed with a pool of human sera (for a concentration 4 to 6 times higher than the found LOB) assayed in 20 replicates for 3 different runs on the Aeroset and Architect instruments. The serum LOQ was determined with a pool of human sera with concentrations around the clinical decision level (1.00 mg/dL). The sera pool was serially diluted with a commercially available analyte free human serum material. Each sample was tested on the Aeroset and the Architect in replicates of 10. The sponsor's acceptance criterion was a total error no greater than 15% (defined by the sponsor as %bias + 2X %CV). The detection limits study supported the sponsor's measuring range claims of 0.1-40.0

mg/dL for serum samples.

Serum results:

Analytical Item	Instrument	Sample	N	mg/dL
LoB	Aeroset	Saline	60	0.0097
LoB	Aeroset	Negative serum	60	0.0154
LOD	Aeroset	Low Serum	60	0.0589
LOQ	Aeroset	Serum	10	0.092
LoB	C8000	Saline	60	0.0076
LoB	C8000	Negative serum	60	0.0086
LOD	C8000	Low serum	60	0.0523
LOQ	C8000	Serum	10	0.092

ii.) A detection limit study was performed according to the CLSI EP17A guideline for the urine samples. The urine LOB was determined by assaying saline in replicates of 20 for 3 different runs on the Aeroset and Architect instruments. The urine LOD was determined by assaying human urine that was diluted with saline (for a creatine concentration around 5 to 6 times higher than the found LOB) and run in 20 replicates in 3 different runs on the Aeroset and Architect instruments. The urine LOQ was determined with two human urine samples with a concentration about 40 mg/dL. The samples were serially diluted with saline to obtain two set of samples with decreased concentrations of creatinine and run in replicated of 10 on the Aeroset and Architect instruments. The detection limits study supported the sponsor's measuring range claims of 2.5-400.0 mg/dL for the urine samples.

Urine results:

Analytical Item	Instrument	Sample	N	mg/dL
LoB	Aeroset	Saline	60	0.097
LOD	Aeroset	Diluted urine	60	0.676
LOQ	Aeroset	Urine	10	2.02
LoB	C8000	Saline	60	0.061
LOD	C8000	Diluted urine	60	0.671
LOQ	C8000	Urine	10	1.74

e. Analytical specificity:

The MULTIGENT Creatinine (Enzymatic) Assay was evaluated for

interferences caused by bilirubin (conjugated and unconjugated), hemoglobin, triglyceride (intralipid), creatine, ascorbic acid, and glucose in serum samples. The MULTIGENT Creatinine (Enzymatic) Assay was also evaluated for interferences caused by ascorbic acid, glucose, hemoglobin, conjugated bilirubin, protein (albumin) and pH in urine samples. The following substances demonstrated no significant bias as defined by the sponsor as +/- 8% difference between the interferent result and the unspiked result.

MULTIGENT Creatinine (Enzymatic)
Serum – Endogenous Interferent Summary

Interfering Substance	Interfering Substance Concentration	Target (mg/dL)	Observed (mg/dL)	% Recovery	% Interference at 1 mg/dL
Bilirubin (conjugated)	39.6 mg/dL	1.09	1.01	92.6%	-8.0%
Bilirubin (unconjugated)	46.2 mg/dL	0.99	0.94	94.9%	-5.0%
Hemoglobin	1000 mg/dL	1.044	0.97	92.9%	-7.4%
Triglyceride*	2,000 mg/dL	0.981	0.94	95.8%	-4.1%
Creatine	100 mg/dL	1.16	1.21	104.3%	+5.0%
Ascorbic Acid	120 mg/dL	1.16	1.09	94.0%	-7.0%
Glucose	6,000 mg/dL	1.15	1.10	95.7%	-5.0%

MULTIGENT Creatinine (Enzymatic)
Urine – Endogenous Interferent Summary

Interfering Substance	Maximum Interfering Substance Concentration	Target (mg/dL)	Observed (mg/dL)	% Recovery
Ascorbic Acid	250 mg/dL	78.86	79.29	100.5%
Glucose	3,000 mg/dL	81.71	78.98	96.7%
Hemoglobin	1,000 mg/dL	80.90	83.85	103.6%
Conjugated Bilirubin	400 mg/dL	81.42	76.00	93.4%
Proteins (albumin)	300 mg/dL	78.41	80.93	103.1%

The sponsor conducted a urine preservative study to determine compatibility of different preservatives that may be used for urine sample collection with the device. The sponsor determined that the following seven preservatives at the stated concentrations caused no interferences.

- Boric acid to 1000 mg/dL
- Hydrochloric acid (6N) to 5 mL/dL

• Acetic acid (8.5N) to 10 mL/dL

• Nitric acid (6N) to 6 mL/dL

• Sodium Carbonate to 1.5 g/dL

• Sodium Oxalate to 70 mg/dL

• Sodium Fluoride to 500 mg/dL

The sponsor conducted a drug interferent study with the MULTIGENT Creatinine (Enzymatic) Assay. The following drugs, when spiked into serum or urine samples were tested at a low and high level and the only one that interfered was alpha-methyldopa in serum. This is noted in the package insert.

Summary of Drug Interference Results – Serum

Drug Name	Drug Units	Low Drug Conc.	Maximum %Bias	Pass Fail	High Drug Conc.	Maximum% Bias	Pass Fail
Acetaminophen	µmol/L	132.4	-1.2%	Pass	See Note 1 below.		
Acetazolamide	µmol/L	270	0.6%	Pass	400	0.6%	Pass
Acetylsalicylic acid	mmol/L	3.62	-1.7%	Pass	5	-0.8%	Pass
Ascorbic acid	µmol/L	342	0.8%	Pass	500	0.8%	Pass
Cefazolin	µmol/L	2643	-0.8%	Pass	4000	-2.5%	Pass
Chlorothiazide	µmol/L	67.6	2.5%	Pass	100	2.5%	Pass
Cimetidine	µmol/L	252	1.7%	Pass	500	0.0%	Pass
Digoxin	nmol/L	7.8	-0.8%	Pass	10	-0.8%	Pass
Furosemide	µmol/L	181	-0.8%	Pass	250	-0.8%	Pass
Gliclazide	µmol/L	100	2.5%	Pass	200	1.6%	Pass
Ibuprofen	µmol/L	2425	-1.7%	Pass	5000	-1.7%	Pass
Phenidione	µmol/L	75	2.5%	Pass	150	1.6%	Pass
Ranitidine	µmol/L	19.1	0.8%	Pass	30	-0.8%	Pass
Spironolactone	µmol/L	1.44	-0.8%	Pass	3	-0.8%	Pass
Triamterene	µmol/L	35	-0.8%	Pass	50	-0.8%	Pass
Alpha-methyldopa	***µmol/L***	***71***	***-20.8%***	***Fail***	***100***	***-25.8%***	***Fail***
Dexamethasone	µmol/L	1.53	-1.7%	Pass	3	-0.8%	Pass
Nitrofurantoin	µmol/L	16.8	-0.8%	Pass	30	-0.8%	Pass

Note 1: Due to the low solubility of acetaminophen in water, only one concentration was tested.

Summary of Drug Interference Results – Urine

Drug Name	Drug Units	Drug Conc.	Maximum %Bias	Pass/ Fail	Drug Conc.	Maximum %Bias	Pass/ Fail
Acetaminophen	µmol/L	132.4	-3.2%	Pass	See Note 1 below.		
Acetazolamide	µmol/L	270	-2.2%	Pass	400	-2.1%	Pass
Acetylsalicylic acid	mmol/L	3.62	1.2%	Pass	5	0.5%	Pass
Ascorbic acid	µmol/L	342	2.5%	Pass	500	2.9%	Pass
Cefazolin	µmol/L	2643	3.9%	Pass	4000	1.0%	Pass
Chlorothiazide	µmol/L	67.6	2.2%	Pass	100	2.7%	Pass
Cimetidine	µmol/L	252	1.7%	Pass	500	1.7%	Pass
Digoxin	nmol/L	7.8	2.0%	Pass	10	1.7%	Pass
Furosemide	µmol/L	181	-0.9%	Pass	250	1.2%	Pass
Gliclazide	µmol/L	100	-3.2%	Pass	200	0.9%	Pass
Ibuprofen	µmol/L	2425	1.5%	Pass	5000	2.9%	Pass
Phenidione	µmol/L	75	-3.2%	Pass	150	-3.0%	Pass
Ranitidine	µmol/L	19.1	1.3%	Pass	30	1.2%	Pass
Spironolactone	µmol/L	1.44	-0.5%	Pass	3	-1.5%	Pass
Triamterene	µmol/L	35	-3.1%	Pass	50	0.9%	Pass
Alpha-methyldopa	µmol/L	71	1.0%	Pass	100	1.2%	Pass
Dexamethasone	µmol/L	1.53	0.3%	Pass	3	0.9%	Pass
Nitrofurantoin	µmol/L	16.8	1.6%	Pass	30	-1.8%	Pass

Note 1: Due to the low solubility of acetaminophen in water, only one concentration was tested.

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 and available enzymatic method as a reference on both instruments for serum and urine. The chart below lists the linear equations, ranges, matrix and instruments.

i.) The serum method comparison contained eighty native samples ranging from 0.320 to 19.700 mg/dL and fourteen spiked samples that ranged from 20.91 to 39.15 mg/dL. Results of the method comparison study were shown below:

MULTIGENT Creatinine (Enzymatic) – Serum
Method Comparison

Regression Parameter	AEROSET vs. Hitachi	ARCHITECT vs. Hitachi	ARCHITECT vs. AEROSET
Slope	1.00 (0.992 to 1.007)	1.011 (1.003 to 1.019)	1.028 (1.003 to 1.018)
Y – Intercept	-0.025 (-0.222 to 0.082)	-0.100 (-0.205 to 0.005)	-0.079 (-0.182 to 0.023)
Correlation Coefficient	.999	0.999	.999
Range of all samples tested (mg/dL)	0.32 to 38.58	0.32 to 38.58	0.31 to 39.24
Std. Error of estimate (Sy/X)	0.349	0.381	0.371
Average Bias (mg/dL)	-0.019 (-0.090 to 0.053)	-0.006 (-0.86 to 0.075)	0.013 (-0.066 to 0.091)
N	94	94	94

ii.) The urine method comparison study contains 60 native samples ranging from 5.98 to 398.26 mg/dL collected from volunteers. Samples over 20 mg/dL are automatically diluted x10 by the ARCHITECT and AEROSET analyzers.

MULTIGENT Creatinine (Enzymatic) – Urine
Method Comparison

Regression Parameter	AEROSET vs. Hitachi	ARCHITECT vs. Hitachi	ARCHITECT vs. AEROSET
Slope	0.964 (0.955 to 0.973)	0.986 (0.980 to 0.992)	1.022 (1.015 to 1.028)

Y – Intercept	1.027 (-0.205 to 2.258)	0.488 (-0.302 to 1.278)	-0.487 (-1.371 to 0.397)
Correlation Coefficient	0.999	1.000	1.000
Range of samples tested (mg/dL)	5.98 to 398.26	5.98 to 398.26	6.06 to 378.02
Std. Error of estimate (Sy/X)	2.867	1.839	2.046
Average Bias (mg/dL)	-2.924 (-3.991 to -1.856)	1.079 (-1.641 to -0.517)	1.845 (1.152 to 2.538)
N	60	60	60

b. Matrix comparison:

A matrix comparison study was conducted to assess the acceptability of 5 different blood collection tube types. Li-heparin plasma (without gel), Li-heparin plasma (with gel barrier), Na-heparin plasma, Serum (with gel barrier), and EDTA plasma were tested against a serum tube (without gel). The creatinine samples (22 native and 49 spiked) ranged from 0.49 to 36.23 mg/dl from 71 subjects were used for the study. The sponsors acceptance criterion is a slope between 0.95 to 1.05 and a correlation coefficient greater than 0.970. The following table supports the usage of lithium heparin (with or without gel barrier), sodium heparin and SST for sample collection for the Multigent Creatinine (enzymatic) assay. However, EDTA returned a bias of -9.1% and is not a recommended anticoagulant. This is noted in the package insert.

Y	Li-heparin	Li-heparin (Gel barrier)	Na-heparin	Serum (Gel barrier)
Slope	1.002 (0.984 to 1.020)	0.993 (0.979 to 1.006)	0.978 (0.964 to 0.992)	1.000 (0.991 to 1.009)
Y-intercept	0.019 (-0.273 to 0.311)	-0.009 (-0.223 to 0.206)	0.124 (-0.101 to 0.350)	0.024 (-0.118 to 0.166)
Correlation Coefficient	0.997	0.998	0.998	0.999
Range (mg/dL)	0.49 to 36.23	0.49 to 36.23	0.49 to 36.23	0.49 to 36.23
N	71	71	71	71

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:

   Serum/Plasma[1]

	Range (mg/dL)	Range (umol/L)
Male	0.73 to 1.18	64 to 104
Female	0.55 to 1.02	49 to 90

   Urine[1]

	Adult Male	Adult Female
24- Hour Excretion	11.1 to 27.9 mg/kg/day (98 to 247 umol/kg/day)	9.8 to 24.7 mg/kg/day (87 to 218 umol/kg/day)
	870 to 2410 mg/day (7.7 to 21.3 mmol/day)	670 to 1590 mg/day (5.9 to 14.1 mmol/day)
Average Concentration *	58 to 161 mg/dL (5.1 to 14.2 mmol/L)	45 to 106 mg/dL (3.9 to 9.4 mmol/L)
Creatinine Clearance	61 to 147 mL/min/1.73 m^2 BSA (1.02 to 2.45 mL/sec/1.73 m^2 BSA)	59 to 151 mL/min/1.73 m^2 BSA (0.98 to 2.52 mL/sec/1.73 m^2 BSA)

   * Concentration is based on a daily urine output of 1.5L.

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.