510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K192730

B Applicant

BioSystems S.A.

C Proprietary and Established Names

CALCIUM-CRESOLPHTHALEIN, GLUCOSE, UREA/BUN-UV

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CHW	Class II	21 CFR 862.1145 - Calcium Test System	CH - Clinical Chemistry
CGA	Class II	21 CFR 862.1345 - Glucose test system	CH - Clinical Chemistry
CDQ	Class II	21 CFR 862.1770 - Urea nitrogen test system	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Calcium, Glucose and Urea/BUN (blood urea nitrogen)

C Type of Test:

Calcium, Glucose and Urea/BUN are quantitative photometric assays.

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

CALCIUM-CRESOLPHTHALEIN: Reagent for the measurement of calcium concentration in human serum, plasma or urine. The obtained values are useful as an aid in the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany (intermittent muscular contractions or spasms). This reagent is for use in the BioSystems BA analyzers. Only for in vitro use in the clinical laboratory.

GLUCOSE: Reagent for the measurement of glucose concentration in human serum and plasma. The obtained values are useful as an aid in the diagnosis and treatment of the diabetes mellitus. This reagent is for use in the BioSystems BA analyzers. Only for in vitro use in the clinical laboratory.

UREA/BUN - UV: Reagent for the measurement of urea concentration in human serum, plasma or urine. The obtained values are useful as an aid in the diagnosis of certain renal and metabolic diseases. This reagent is for use in the BioSystems BA analyzers. Only for in vitro use in the clinical laboratory.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

BioSystems BA400

IV Device/System Characteristics:

A Device Description:

Reagents are provided ready to use.

CALCIUM-CRESOLPHTHALEIN: Reagent for the measurement of calcium concentration in human serum, plasma or urine. The CALCIUM-CRESOLPHTHALEIN assay consists of the following reagents:

- Ethanolamine 900 mmol/L.

- Reagent: O-Cresolphthalein Complexone 0.3 mmol/L, 8 hydroxyquinoline 28 mmol/L, hydrochloric acid 100 mmol/L.

The GLUCOSE assay consists of the following reagents:

Phosphate 100 mmol/L, phenol 5 mmol/L, glucose oxidase > 10 U/mL, peroxidase >1 U/mL, 4-aminoantipyrine 0.4 mmol/L, pH 7.5

The UREA/BUN - UV assay consists of the following reagents:

- Tris 100 mmol/L, 2-oxoglutarate 5.6 mmol/L, urease > 140 U/mL, glutamate dehydrogenase > 140 U/mL, ethyleneglicol 220 g/L, sodium azide 0.95, pH 8.0.
- NADH 1.5 mmol/L, sodium azide 9.5 g/L.

B Principle of Operation:

The CALCIUM-CRESOLPHTHALEIN reagent is a photometric assay in which Calcium in the sample reacts with o-cresolphthalein complexone (o-CPC) forming a colored complex that can be measured by spectrophotometry.

The GLUCOSE reagent is a photometric assay in which glucose is oxidized by glucose-oxidase to gluconate and hydrogen peroxide. The hydrogen peroxide is then oxidized by peroxidase in the presence of 4-aminoantipyrine and phenol to form a colored complex that can be measured by spectrophotometry.

The UREA-BUN/UV reagent is a photometric assay in which BUN-Urea is hydrolyzed by urease to produce ammonia and carbon dioxide. The ammonia reacts with 2–oxoglutarate in the presence of NADH to yield glutamate and NAD+.

Modes of Operation	Yes	No
Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?	☐	☒
Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?	☐	☒
Software		
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.	☐	☒

V Substantial Equivalence Information:

A Predicate Device Name(s):

CALCIUM GEN. 2
GLUCOSE HK GEN. 3
Urea/BUN

B Predicate 510(k) Number(s):

K100853

Comparison with Predicate(s):

Device & Predicate Device(s):	K192730	K100853
Device Trade Name	CALCIUM-CRESOLPHTHALEIN	CALCIUM GEN. 2
General Device Characteristic Similarities		
Intended Use/Indications For Use	Reagent for the measurement of calcium concentration	Same
Measurand	Calcium	Same
Sample type	Serum, Lithium Heparin plasma or urine.	Same
General Device Characteristic Differences		
Method	O-CRESOLPHTHALEIN COMPLEXONE	NM-BAPTA
Measuring range	Serum/plasma: 0.80 - 20 mg/dL Urine: 3.97-30 mg/dL	Serum/plasma: 0.80 - 20.1 mg/dL Urine: 0-140 mg/dL

Device & Predicate Device(s):	K192730	K100853
Device Trade Name	GLUCOSE	GLUCOSE HK GEN. 3
General Device Characteristic Similarities		
Intended Use/Indications For Use	Reagent for the measurement of glucose concentration	Same
Measurand	Glucose	Same
General Device Characteristic Differences		
Method	Oxidase	Hexokinase
Sample type	Serum or Lithium Heparin plasma	Serum, plasma, urine or cerebrospinal fluid

Device & Predicate Device(s):	K192730	K100853
Measuring range	Serum/plasma: 2.0 - 500 mg/dL	Serum/plasma: 2.0 - 750 mg/dL

Device & Predicate Device(s):	K192730	K100853
Device Trade Name	UREA-BUN/UV	Urea/BUN
General Device Characteristic Similarities		
Intended Use/Indications For Use	Reagent for the measurement of urea concentration	Same
Measurand	Urea	Same
Sample type	Serum, Lithium Heparin plasma or urine.	Same
Method	Urease/Glutamate Dehydrogenase	Same
General Device Characteristic Differences		
Measuring range	Serum/plasma: 10 mg/dL–240 mg/dL Urine: 635-12000 mg/dL	Serum/plasma: 3.0-240 mg/dL Urine: 6-12000 mg/dL

VI Standards/Guidance Documents Referenced:

CLSI - EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Third Edition.

CLSI - EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.

CLSI - EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Internal precision studies were performed according to the CLSI EP5-A3 guideline. For CALCIUM-CRESOLPHTHALEIN, GLUCOSE and UREA/BUN - UV, three levels of commercial biochemistry control serum (human serum matrix) Level I, II and III or Urine,

Level I, II and III were tested on two runs per day, two measurements per run, for twenty days with a total of 80 observations using the BioSystems BA400 analyzer. The results of the precision studies are summarized in the tables below:

CALCIUM-CRESOLPHTHALEIN:

Matrix	Samples	n	Mean (mg/dL)	Repeatability		Total	
				SD	CV%	SD	CV%
Serum	Level 1	80	5.10	0.1	1.6	0.1	2.9
	Level 2	80	10.0	0.2	2.2	0.3	2.7
	Level 3	80	14.0	0.1	1.0	0.3	1.9
Urine	Level 1	80	7.95	0.2	1.9	0.3	3.3
	Level 2	80	15.5	0.2	1.2	0.4	2.3
	Level 3	80	26.6	0.3	1.0	0.9	3.5

GLUCOSE:

Matrix	Samples	n	Mean (mg/dL)	Repeatability		Total	
				SD	CV%	SD	CV%
Serum	Level 1	80	48.6	0.3	0.7	0.4	0.9
	Level 2	80	211	0.9	0.4	2.2	1.0
	Level 3	80	389	0.9	0.2	2.4	0.6

UREA/BUN - UV:

Matrix	Samples	n	Mean (mg/dL)	Repeatability		Total	
				SD	CV%	SD	CV%
Serum	Level 1	80	26.8	1.0	3.6	1.3	5.0
	Level 2	80	137	1.5	1.1	2.3	1.7
	Level 3	80	172	2.2	1.3	3.4	2.0
Urine	Level 1	80	1003	39.5	3.9	45.5	4.5
	Level 2	80	1918	44.6	2.3	59.5	3.1
	Level 3	80	7293	87.3	1.2	180	2.5

2. Linearity:

Linearity studies were conducted according to the CLSI EP06-A guideline. Eleven levels of dilutions were prepared by mixing different proportions of samples with high and low concentration of each analyte. Samples were analyzed on one BA400 instrument in duplicate. The results of the regression analysis are shown below:

Analyte	Matrix	Slope	Intercept	r^2	Range Conc. Tested (mg/dL)	Claimed range (mg/dL)
CALCIUM-CRESOLPH-THALEIN	Serum	1.004	-0.42	0.999	0.0 – 20.0	0.80 - 20.0
	Urine	1.010	-0.119	1.000	0.0 – 30.0	3.97 – 30.0

Analyte	Matrix	Slope	Intercept	r^2	Range Conc. Tested (mg/dL)	Claimed range (mg/dL)
GLUCOSE	Serum	1.002	2.61	1.000	0.0 - 500	2.0 - 500
UREA/BUN - UV	Serum	1.004	-0.42	0.999	0.0 - 240	10.0 - 240
	Urine	0.996	0.19	0.999	0.0 - 12000	635 - 12000

The linearity studies support the sponsor's claimed measuring ranges as described in the table above.

3. Analytical Specificity/Interference:

Interference studies were performed for CALCIUM-CRESOLPHTHALEIN, GLUCOSE and UREA/BUN – UV. Specimens consisted of human serum and urine representing low and high concentrations of the analyte, with and without the substance tested for interference. Serum samples for the CALCIUM-CRESOLPHTHALEIN assay were tested at concentrations of approximately 9.7 and 13.8 mg/dL, and urine samples were tested at concentrations of 5.7 and 14.9 mg/dL. Serum samples for the GLUCOSE assay were tested at concentrations of approximately 87 and 219 mg/dL. Serum samples for the UREA/BUN - UV assay were tested at concentrations of approximately 21.9 and 117 mg/dL, and urine samples were tested at concentrations of 866 and 1638 mg/dL. Samples were spiked with increasing concentrations of the potential interferents and analyzed in duplicate using the BioSystems BA400 analyzer. Interference was calculated as: (b-a)/a, where a and b are the concentration of measurand found in samples without (a) and with (b) interferent. The sponsor stated that interference was considered to be non-significant if the difference between the samples with and without interferent was within 10%.

The results of the interference studies are summarized in the table below.

Analyte	Interferent	Highest concentration tested that did not show significant interference
CALCIUM-CRESOLPHTHALEIN	Bilirubin	30 mg/dL
	Hemoglobin	500 mg/dL
	Triglycerides	1300 mg/dL
GLUCOSE	Bilirubin	12 mg/dL
	Hemoglobin	604 mg/dL
	Triglycerides	222 mg/dL
UREA/BUN-UV	Bilirubin	30 mg/dL
	Hemoglobin	500 mg/dL
	Triglycerides	1625 mg/dL

The following limitation is stated in the GLUCOSE device labeling:

This device has significant positive interference with triglycerides at levels above 222 mg/dL. Do not use lipemic samples with this assay.

Exogenous interferences:

Analyte	Matrix	Interferent	Highest concentration tested that did not show significant interference
CALCIUM-CRESOLPHTHALEIN	Serum	Acetaminophen	20 mg/dL
		Ascorbic Acid	30 mg/dL
		Acetylsalicylic Acid	70 mg/dL
	Urine	Ascorbic Acid	30 mg/dL
GLUCOSE	Serum	Acetaminophen	20 mg/dL
		Uric Acid	20 mg/dL
		Ascorbic Acid	6 mg/dL
UREA/BUN-UV	Serum	Acetaminophen	20 mg/dL
		Ascorbic Acid	30 mg/dL
		Acetylsalicylic Acid	70 mg/dL
	Urine	Ascorbic Acid	30 mg/dL

4. Assay Reportable Range:

Analyte	Matrix	Claimed range (mg/dL)
CALCIUM-CRESOLPHTHALEIN	Serum	0.80 - 20.0
	Urine	3.97 – 30.0
GLUCOSE	Serum	2.0 - 500
UREA/BUN-UV	Serum	10.0 - 240
	Urine	635 - 12000

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Traceability:

The sponsor provided the following information on the traceability of the assays:

Assay	Traceability
CALCIUM-CRESOLPHTHALEIN	SRM 956 (NIST) Standard Reference Materials.
GLUCOSE	SRM 965 (NIST) Standard Reference Materials.
UREA/BUN-UV	SRM 909 (NIST) Standard Reference Materials

6. Detection Limit:

Detection capabilities studies for each analyte were evaluated based upon the CLSI EP17-A2 guideline.

Limit of blank (LoB) studies were performed by testing 5 blank samples in replicates of 4 over 3 days, on two lots for a total of 120 observations. LoB was defined as the highest result that can reasonably be expected from a blank sample for a given error probability with α=0.05.

Limit of detection (LoD) studies were performed by testing 5 pools of human serum or urine with analyte concentrations close to expected detection limit for each analyte. Samples were tested in replicates of 4 over 3 days, on two lots for a total of 120 observations. The LoD was estimated based on a probability of error of 5% (β=0.05).

Limit of quantitation (LoQ) studies were performed using 4 to 5 pools of human serum or urine with analytes concentrations closed to the expected LoQ of the corresponding assay. Samples were tested in replicates of 4 over 3 days, on two lots for a total of 120 observations. The sponsor defines LoQ as the lowest concentration of a measurand with a CV ≤10%.

The results of the detection limit studies are presented in the table below:

Assays	Matrix	LoB	LoD	LoQ	Claimed Range
CALCIUM-CRESOLPHTHALEIN	Serum	0.22	0.46	0.80	0.80 - 20.0 mg/dL
	Urine	0.19	0.47	3.97	3.97 - 20.0 mg/dL
GLUCOSE	Serum	0.39	1.09	2.00	2.0 - 500 mg/dL
Urea/BUN-UV	Serum	1.67	3.78	10.0	10.0-240 mg/dL
	Urine	169	356	635	635-12000 mg/dL

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Method comparison studies were conducted by testing native human serum, Lithium Heparin plasma and urine samples (as applicable) on CALCIUM-CRESOLPHTHALEIN, GLUCOSE and UREA/BUN-UV candidate assays on the BA400 analyzer and the predicate devices. To supplement testing across the reportable range of the assays, some samples were altered (spiked or diluted) and used to cover the full measuring range of each analyte.

The results of the regression analysis are summarized below:

Analyte	Specimen Type	N	Slope	Intercept	R	Test range mg/dL	Claimed Measuring Range mg/dL
CALCIUM-CRESOLPH-THALEIN	Serum	153	1.056	-0.57	0.992	0.88 -17.9	0.80 - 20.0
	Li Heparin Plasma	146	1.033	-0.336	0.996	1.20 - 19.8	
	Urine	77	0.97	0.0034	0.995	4.32 - 29.4	3.97 - 30.0
GLUCOSE	Serum	146	1.004	2.10	0.999	8.43 - 485	2.0 - 500

Analyte	Specimen Type	N	Slope	Intercept	R	Test range mg/dL	Claimed Measuring Range mg/dL
	Li Heparin Plasma	127	0.997	0.28	0.996	5.58 - 432	
UREA/BUN - UV	Serum	111	0.99	2.34	0.997	10.8 - 232	10.0 - 240
	Li Heparin Plasma	112	1.00	3.02	0.998	12.4 -238	
	Urine	97	1.057	-22.0	0.998	650-11462	635-12000

2. Matrix Comparison:

   Not applicable. Different sample types were assessed in other analytical studies described above.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The following reference ranges are cited from literature:

CALCIUM-CRESOLPHTHALEIN[(1)]
8.6-10.0 mg/dL (2.15-2.50 mmol/L)
Urine: 100-300 mg/24-h (2.5-7.5 mmol/24-h)

GLUCOSE
Serum and plasma (Adult): 74 -100 mg/dL (4.10-5.60 mmol/L)[(2)]
According to American Diabetes Association)[(3)], elevation of fasting plasma glucose values over 126 mg/dL (7.0 mmol/L) on more than one occasion is diagnostic of diabetes mellitus.

UREA/BUN-UV[2]
Serum and plasma: 14.4 – 48 mg/dL urea, 6 - 20 mg/dL BUN (5.14 – 17.14 mmol/L urea).
Urine: 26-43 g/24-h urea, 12-20 g/24 h BUN (428-714 mmol/24-h urea)

[1]Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 3rd ed. Burtis C.A., Ashwood E.R., Bruns D.E., (WB Saunders Co, 1987).

[2]Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th ed. Burtis C.A., Ashwood E.R., Bruns D.E., (WB Saunders Co, 2012).

[3]American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical care in Diabetes. Diabetes Care 2020 Jan; 43(Supplement 1): S14-S31.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.