510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k170901

B. Purpose for Submission:

New devices

C. Measurand:

Albumin, Alkaline phosphatase, Glucose

D. Type of Test:

Albumin and Alkaline phosphatase: Quantitative, colorimetric
Glucose: Quantitative, enzymatic

E. Applicant:

BioSystems S.A.

F. Proprietary and Established Names:

Albumin
Alkaline Phosphatase (ALP)-AMP
Glucose-Hexokinase
BA400 Analyzer

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CIX	II	21 CFR § 862.1035 Albumin Test System	Clinical Chemistry (75)
CFR	II	21 CFR § 862.1345 Glucose Test System	
CJE	II	21 CFR § 862.1050 Alkaline Phosphatase or isoenzymes test system	
JJE	I	21 CFR § 862.2160, Discrete photometric chemistry analyzer for clinical use	

H. Intended Use:

1. Intended use(s):

   See Indications for use below

2. Indication(s) for use:

   Albumin
   Reagent for the measurement of albumin concentration in human serum or plasma. The obtained values are useful as an aid in the evaluation of protein synthesis of the liver in the chronic liver diseases and for the study of the nutritional status. This reagent is for use in the BioSystems BA analyzers.

   Alkaline Phosphatase (ALP)-AMP
   Reagent for the measurement of alkaline phosphatase (ALP)-AMP concentration in human serum or plasma. The obtained values are useful as an aid in the diagnosis and treatment of hepatobiliary and bone diseases with impaired osteoblastic activity diseases. This reagent is for use in the BioSystems BA analyzers. Only for in vitro use in the clinical laboratory.

   Glucose-Hexokinase
   Reagent for the measurement of glucose concentration in human serum, plasma, urine or cerebrospinal fluid. The obtained values are useful as an aid in the diagnosis and monitoring of the diabetes mellitus. This reagent is for use in the BioSystems BA analyzers. Only for in vitro use in the clinical laboratory.

   BA400
   The BA400 analyser is used to determine analyte concentrations by in vitro biochemical, turbidimetric and electrolyte measurements of human samples of serum, urine, plasma, cerebrospinal fluid or total blood. This device is intended to replace manual analytical procedures by performing automatically various steps such as pipetting, heating, and measuring color intensity.

3. Special conditions for use statement(s):

   This device is intended for prescription use and in vitro diagnostic use only.

4. Special instrument requirements:

   BA400

I. Device Description:

The Albumin assay consist of the following reagent:
Acetate buffer 100 mmol/L, bromocresol green 0.27 mmol/L, detergent, pH 4.1
(package of 10 x60 mL or 4x60 mL)

The Alkaline Phosphatase(ALP)-AMP assay consists of the following reagents:

- 2-Amino-2-methyl-1-propanol 0.4 mol/L, zinc sulfate 1.2 mmol/L, N-hydroxy ethyl ethylene di-amine tri acetic acid 2.5 mmol/L, magnesium acetate 2.5 mmol/L, pH 10.4 (package of 1 x60 mL or 4x60 mL)
- 4-Nitrophenylphosphate 60 mmol/L (package of 1 x15 mL or 4x15 mL)

The Glucose-Hexokinase assay consist of the following reagents:

- Buffer 70 mmol/L, Hexokinase >15 U/mL, NADP >1.5 mM, preservatives, pH 6.9 (package of 1 x60 mL or 4x60 mL)
- Buffer 150 mmol/L, ATP >15 mmol/L, glucose-6-phosphate dehydrogenase >10 U/mL, preservatives, pH 8.9. (package of 1 x15 mL or 4x15 mL)

Analyzer:
The BA400 is a fully automated clinical chemistry analyzer intended for the in vitro quantitative determination of analytes in body fluids.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   cobas 8000 MODULAR Series Analyzer, ALB Gen 2, Alkaline Phosphatase Gen 2, Glucose HK

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

   k100853

3. Comparison with predicate:

BA400 - Similarities and Differences		
Item	Candidate Device BA400 (k170901)	Predicate Device cobas 8000 (k100853)
Intended Use	Fully automated clinical chemistry analyzer intended for the in vitro quantitative/qualitative determination of analytes in body fluids.	Same
Measurement principle	Absorbance photometry	Same
Reagent container and access	Plastic bottles closed vial screwcaps to be opened before placing on the instrument	Same
Configuration	Single analytical unit	Modular

BA400 - Similarities and Differences		
Item	Candidate Device BA400 (k170901)	Predicate Device cobas 8000 (k100853)
Reagent identification	Barcode	Radio frequency identification (RFID)

Albumin - Similarities and Differences		
Item	Candidate Device k170901	Predicate Device k100853
Intended Use	For the quantitative determination of albumin concentration	Same
Assay Method	Bromocresol green	Same
Sample types	Human serum and plasma	Same
Measuring Range	3.6 - 60 g/L	2 - 60 g/L
Reagent storage	Store at 2-8 ºC	Store at 15-25 ºC
On board stability	2 months	4 weeks

Alkaline Phosphatase (ALP)-AMP - Similarities and Differences		
Item	Candidate Device k170901	Predicate Device k100853
Intended Use	For the measurement of alkaline phosphatase (ALP) concentration in human serum or plasma	Same
Measurand	Alkaline phosphatase	Same
Assay Method	2-amino-2-methyl-1-propanol buffer (IFCC)	Same
Sample types	Human serum and plasma	Same
Measuring Range	65.3 - 1200 U/L	5 -1200 U/L

Glucose- Hexokinase - Similarities and Differences		
Item	Candidate Device k170901	Predicate Device k100853
Intended Use	For the measurement of glucose concentration in human serum, plasma, urine or cerebrospinal fluid	Same
Measurand	Glucose	Same
Assay Method	Hexokinase	Same
Sample types	Human serum, plasma urine and CSF	Same
Reagent storage	Store at 2-8 ºC	Same
Measuring Range	6.2 - 750 mg/dL	2 - 750 mg/dL
On board stability	2 months	4 weeks

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

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 - EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition.

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

IEC 61010: Safety Requirements for electrical equipment for measurement, control and laboratory use. Part l : General requirements. Part 2-10 l : Particular Requirements for In Vitro Diagnostic (IVD) Medical Equipment.

L. Test Principle:

The Albumin reagent is a photometric assay in which the albumin in the sample reacts with bromocresol green in acid medium, forming a colored complex that is measured by spectrophotometry.

The Alkaline Phosphatase (ALP)-AMP reagent is a photometric assay in which the alkaline phosphatase (ALP) present in the sample catalyzes the transfer of the phosphate group from 4-nitrophenylphosphate to 2-amino-2-methyl-1-propanol (AMP), liberating 4-nitrophenol. The catalytic concentration is determined from the rate of 4-nitrophenol formation, measured at 405 nm.

The Glucose-Hexokinase reagent is a photometric assay in which glucose in the sample reacts with ATP, in a reaction catalyzed by hexokinase, forming glucose-6-phosphate and ADP. In the coupled reaction catalyzed by glucose-6-phosphate dehydrogenase, glucose-6-phosphate reacts with NADP forming gluconate-6- phosphate and NADPH. The NADPH produced is measured by spectrophotometry.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision studies were conducted following CLSI EP05-A3 guideline. Study was performed by testing three levels of control material (human serum matrix) using the Albumin, Alkaline Phosphatase (ALP)-AMP and Glucose-Hexokinase assays. In addition, three levels of urine and cerebrospinal fluid (CSF) control material were tested using the Glucose-Hexokinase assay.

Samples were analyzed using one BA400 analyzer over 20 days, with 2 runs per day and 2 replicates per specimen (n=80).

The results of the precision study are shown in the table below:

Test	Samples	Mean	Within-run		Total	
			SD	%CV	SD	%CV
Albumin g/L	QC I	8.04	0.39	4.9	0.48	5.9
	QC II	38.4	0.31	0.8	0.46	1.2
	QC III	57.1	0.38	0.7	0.64	1.1
Alkaline Phos U/L	QC I	133.9	1.83	1.4	3.28	2.5
	QC II	204.8	1.84	0.9	3.65	1.8
	QC III	905	7.72	0.9	12.02	1.3
Serum Glucose mg/dL	QC I	46.6	0.34	0.7	0.53	1.1
	QC II	85.2	0.57	0.7	0.82	1.0
	QC III	326	0.99	0.3	2.09	0.6
Urine Glucose mg/dL	UQC I	28.9	0.23	0.8	0.38	1.3
	UQC II	147	0.65	0.4	1.09	0.7
	UQC III	263	1.01	0.4	1.88	0.7
CSF Glucose mg/dL	CSF QC I	50.7	0.57	1.1	0.71	1.4
	CSF QC II	102	0.56	0.5	0.90	0.9
	CSF QC III	420	2.22	0.5	5.23	1.2

b. Linearity/assay reportable range:

Linearity studies were performed according to CLSI EP06-A guideline. Nine levels of dilutions were prepared by mixing different proportions of samples with high and low concentration of the analytes; each samples was tested in duplicate. The summary of the linear regression analysis of the data is below:

Test	**Slope**	**Intercept**	**r^2**	**Range tested**	**Claimed Range**
Albumin (g/L)	0.999	0.755	0.999	0 - 74.2	3.6 - 60
Alk Phos (U/L)	1.010	-2.519	0.999	5.24 - 1232	65.3 - 1200
Glucose (mg/dL) serum	1.023	-1.419	0.999	0 - 836	6.2 - 750
Glucose (mg/dL) urine	1.023	2.450	0.999	0 - 833	6.2 - 750

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

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

The information on the traceability of the assays is provided below:

Analyte	Traceability
Albumin	International standard ERM-DA470/IFCC (IRMM)
Alkaline Phosphatase	Reference system as described by the IFCC Committee on Reference Systems for Enzymes (C-RSE/IFCC), through a BioSystems master calibrator (BMC).
Glucose	International standard SRM 965 (NIST)

d. *Detection limit:*

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

Limit of blank (LoB) studies were performed by testing 5 blank samples. Samples were tested in replicates of 4 over 3 days, using 2 lots of reagents, 5 samples every day, for a total of 120 observations (60 results per lot). 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 pool of human samples with analyte concentrations close to expected detection limit for each analyte. Samples were tested in replicates of 4 over 3 days, using 2 lots of reagents, 5 samples every day, for a total of 120 observations (60 results per lot). LoD was calculated using the following equation: $LoD = LoB + Cp \times SD_L$.

Limit of Quantitation studies were performed using 4 to 5 pools of low level samples with analytes concentrations closed to the expected LoQ of the corresponding assay. Samples were tested in replicates of 4 over 3 days, using 2 lots of reagents, 5 samples every day, for a total of 120 observations (60 results per lot). The sponsor defines LoQ as the lowest concentration with an imprecision of $\leq$10% for albumin and alkaline phosphatase, glucose in urine and CSF, and $\leq$5% for glucose in serum.

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

	Albumin (g/dL)	Alkaline phosphatase U/L	Glucose (mg/dL)		
			Serum/plasma	Urine	CSF
LoB	0.677	10.6	0.179	0.18	0.18
LoD	1.34	17.2	0.728	0.55	0.60
LoQ	3.6	65.3	6.20	5.4	4.07
Assay Range	3.6 - 60	65.3 - 1200	6.2 - 750	6.2 - 750	6.2 - 750

e. Analytical specificity:

An interference study was performed in accordance with CLSI EP07-A2 guideline. For all 3 assays (Albumin, Alkaline Phosphatase (ALP)-AMP, and Glucose-Hexokinase) two human serum samples with two different analyte concentrations were spiked with increasing concentrations of the potential interferents and analyzed in duplicate. Interference was calculated as: (b-a)/a, where a and b are the concentration of measurand found without (a) and with (b) interferent. The sponsor states that interference is considered to be non-significant if the difference between the samples with and without interferent are within 10%.

The results of the highest concentration tested without significant interference are summarized in the table below.

Analyte	Interferent	Highest concentration tested that did not show significant interference
Albumin	Bilirubin	30 mg/dL
	Hemoglobin	400 mg/dL
	Triglycerides	655 mg/dL
Alkaline phosphatase	Bilirubin	30 mg/dL
	Hemoglobin	500 mg/dL
	Triglycerides	1628 mg/dL
Glucose-serum	Bilirubin	30 mg/dL
	Hemoglobin	500 mg/dL
	Triglycerides	1301 mg/dL
	Acetaminophen	20 mg/dL
	Uric acid	20 mg/dL
	Ascorbic acid	6 mg/dL
Glucose-Urine	Specific gravity	1.033
	pH	12.3
	Urea	5888 mg/dL

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were conducted by testing a minimum of 100 unmodified human serum and lithium heparin plasma samples with analyte concentrations within the analytical ranges of albumin, alkaline phosphatase and glucose assays on the BA400 analyzer and the Roche cobas 8000 (predicate device).

In addition, 64 unmodified urine samples and 113 cerebrospinal fluid samples were tested for glucose on the candidate and predicate test systems. The results of the Passing-Bablok regression analysis are summarized below:

Analyte	Specimen Type	N	Slope	Intercept	R	Test range	Claimed Measuring Range
Albumin (g/L)	serum	118	0.996	0.080	0.993	7.1 – 56.7	3.6 - 60
	plasma	127	1.030	-0.815	0.988	7.9 - 58	
ALP (U/L)	serum	139	0.992	-3.796	0.999	25.8 - 1186	65.3 - 1200
	plasma	130	1.009	-5.247	0.999	33.6 - 1150	
Glucose (mg/dL)	serum	151	0.979	0.9754	0.999	13 - 740	6.2 - 750
	plasma	134	0.992	-2.819	0.998	11.2 - 735	
	urine	64	1.029	1.704	1.000	8.1 - 731	
	CSF	113	1.005	-3.017	0.999	7.2 - 676	

Method comparison data supports that serum and lithium heparin plasma are acceptable samples for the Albumin and Alkaline Phosphatase (ALP)-AMP assays. The Glucose-Hexokinase assay can be used with serum, lithium heparin plasma, urine and CSF specimens.

b. Matrix comparison:

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

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:

   Reference ranges for albumin, alkaline phosphatase and glucose are cited from literature:

   Albumin[1]:
   Newborn 2 to 4 days: 28-44 g/L
   4 days to 14 years: 38-54 g/L
   Adult: 35-52 g/L
   > 60 years: 32-46 g/L

   Alkaline phosphatase [2]:
   Men: 43 – 115 U/L
   Women: 33 – 98 U/L

   Glucose[1]:
   Serum and plasma: 60 - 100 mg/dL
   Urine: Random urine: 1 - 15 mg/dL
   24-hour urine: < 0.5 g/24-h
   Cerebrospinal fluid: Adult: 40 - 70 mg/dL

   [1]Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th ed. Burtis CA, Ashwood ER, Bruns DE. WB Saunders Co, 2012.

   [2]Infusino, I., Frusciante, E., Braga, F., et al. Progress and impact of enzyme measurement standardization. Clin Chem Lab Med 2017; 55:334-340.

N. Instrument Name:

BA400

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
   Yes ___X___ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
   Yes _____ or No ___X___

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___X___ or No _____

3. Specimen Identification:
   Samples can be identified by barcode reading, manually entering code or instrument auto numbering. The specimen is handled by automatic aspiration from the direct open tube located onto the sample tray.

4. Specimen Sampling and Handling:
   The Albumin and Alkaline Phosphatase assays are for use with serum and plasma samples. Glucose assay is for use with serum, plasma, urine and CSF samples.

5. Calibration:
   The calibration is performed with commercial calibration materials. Frequency of calibration varies according to the analytes, and is recommended after reagent lot change or as required by quality control procedures.

6. Quality Control:
   The manufacturer recommends using commercial quality control materials to verify accuracy of the measurement procedures. Each laboratory should establish its own internal quality control scheme.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Software documentation was reviewed and found acceptable.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

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