Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K191245

B Applicant

Horiba Abx Sas

C Proprietary and Established Names

Yumizen C1200 ALP, Yumizen C1200 Albumin

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CJE	Class II	21 CFR 862.1050 - Alkaline Phosphatase Or Isoenzymes Test System	CH - Clinical Chemistry
CIX	Class II	21 CFR 862.1035 - Albumin test system	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New devices

B Measurand:

Alkaline phosphatase (ALP)
Albumin

C Type of Test:

ALP - Quantitative; kinetic photometric
Albumin - Quantitative; colorimetry

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Yumizen C1200 ALP reagent is intended for the quantitative in vitro diagnostic determination of alkaline phosphatase in human serum and plasma based on a kinetic photometric test using p-nitrophenylphosphate. Measurements of alkaline phosphatase or its isoenzymes are used in the diagnosis and treatment of liver, bone, parathyroid, and intestinal diseases.

Yumizen C1200 Albumin reagent is intended for the quantitative in vitro diagnostic determination of albumin in human serum and plasma by colorimetry. Albumin measurements are used in the diagnosis and treatment of numerous diseases involving primarily the liver or kidneys.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Not for point-of-care use

D Special Instrument Requirements:

Yumizen C1200

IV Device/System Characteristics:

A Device Description:

The Yumizen C1200 ALP assay consists of the following reagents:

Reagent 1: 1.1 mol/L 2-amino-2-methyl-1-propanol (pH 10.4), 2 mmol/L magnesium acetate, 0.5 mmol/L zinc sulphate, and 2.5 mmol/L HEDTA

Reagent 2: 80 mmol/L p-Nitrophenylphosphate

The Yumizen C1200 Albumin assay consists the following reagents: 30 mmol/L citrate buffer (pH 4.2) and 0.26 mmol/L bromocresol green.

B Principle of Operation:

ALP- Quantitative measurement of the catalytic activity of alkaline phosphatase in human serum and plasma in accordance with a standardized method. In the presence of magnesium and zinc ions, p-nitrophenyl phosphate is cleaved by alkaline phosphatases in the sample into phosphate and p-nitrophenol. The p-nitrophenol released is directly proportional to the catalytic ALP activity. It is determined by measuring the increase in absorbance.

Albumin- Colorimetric test for the quantitative determination of albumin in serum and plasma using Bromocresol Green dye binding procedure. At pH 4.20, in succinate buffer and with a non-ionic surfactant, the bromocresol green (BCG) fixes itself selectively to the albumin present in the sample, producing a blue color which is measured at 628 nm. The intensity of the coloring is directly proportional to the albumin concentration.

V Substantial Equivalence Information:

A Predicate Device Name(s):

ALP IFCC Gen.2
ABX PENTRA Albumin CP

B Predicate 510(k) Number(s):

k171080
k060434

C Comparison with Predicate(s):

ALP

Device & Predicate Device(s):	K191245	K171080
Device Trade Name	Yumizen C1200 ALP	ALP IFCC Gen.2
General Device Characteristic Similarities		
Intended Use/Indications For Use	For quantitative *in vitro* determination of Alkaline Phosphatase (ALP) in serum or plasma.	Same
Matrix	Serum, plasma in lithium heparin	Same
Reagent format	Liquid	Same
Measurement	Quantitative	Same
Reference range	40-129 U/L (Men) 35-104 U/L (Women)	Same
General Device Characteristic Differences		
Instrument	Yumizen C1200	Cobas Integra systems
Reagent On-board Stability	1 week after opening	4 weeks on-board at 10-15°C
Measuring Range	6.0-1200 U/L	3.0-1200 U/L
Automatic post-dilution:	Can measure ALP concentrations up to 4800 U/L with the automatic postdilution.	Results from samples diluted using the re-run function are automatically multiplied by a factor of 5.

ALBUMIN

Device & Predicate Device(s):	K191245	K060434
Device Trade Name	Yumizen C1200 Albumin	ABX Pentra Albumin CP
General Device Characteristic Similarities		
Intended Use/Indications For Use	For the quantitative in vitro diagnostic determination of albumin in human serum and plasma by colorimetry. Albumin measurements are used in the diagnosis and treatment of numerous diseases involving primarily the liver or kidneys.	Same
Matrix	Serum, plasma in lithium heparin	Same
Reagent format	Liquid	Same
Measurement	Quantitative	Same
Method	Colorimetry	Same
Measuring Range	0.46-5.60 g/dL	Same
Automatic post-dilution:	Up to 11.20 g/dL	Same
General Device Characteristic Differences		
Instrument	Yumizen C1200	ABX Pentra 400 Clinical Chemistry Analyzer
Sample Volume	1µL/test	2µL
Reagent On board Stability	Stable for 6 weeks.	Stable for 83 days (11 weeks)
Calibration Stability	6 weeks	14 days

VI Standards/Guidance Documents Referenced:

CLSI Guidelines:

- **CLSI EP05-A3:** Evaluation of Precision of Quantitative Measurement Procedures– Third Edition – October 2014
- **CLSI EP17-A2:** Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures – Second Edition - June 2012
- **CLSI EP06-A:** Evaluation of the Linearity of Quantitative measurement Procedures A Statistical Approach – First Edition – April 2003
- **CLSI C28-A3:** Defining, Establishing, and Verifying Reference Intervals in the Clinical laboratory- Third Edition – November 2008
- **CLSI EP25-A**: Evaluation of Stability of In Vitro Diagnostic reagents

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Repeatability studies were conducted by testing 2 control materials (Yumizen C1200 N Multi Control and Yumizen C1200 P Multi Control) and low, mid, and high serum samples (5 specimens for ALP and 3 specimens for albumin). For each sample, 20 replicates were measured. For the repeatability study, samples were analyzed in a single run on a single instrument using a single lot of reagent for each assay.

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

Test	Samples	N	Mean	Within-run	
				SD	%CV
ALP (U/L)	Control 1	20	80.60	0.43	0.54
	Control 2	20	198.20	1.61	0.81
	Sample 1	20	10.64	0.37	3.49
	Sample 2	20	19.34	0.21	1.07
	Sample 3	20	52.11	0.47	0.91
	Sample 4	20	386.68	1.27	0.33
	Sample 5	20	1155.16	5.92	0.51
Albumin (g/L)	Control 1	20	39.26	0.15	0.37
	Control 2	20	49.23	0.32	0.64
	Low Sample	20	20.11	0.12	0.60
	Mid Sample	20	39.89	0.26	0.64
	High Sample	20	55.82	0.28	0.51

Precision studies to evaluate lot-to-lot reagent variability were conducted following CLSI EP05-A3 guideline. Pooled samples of sera with concentration spanning the analytical measuring range (5 specimens for ALP and 3 specimens for albumin) and 2 controls (Yumizen C1200 N Multi Control and Yumizen C1200 P Multi Control) were tested in triplicate with 2 runs per day over 5 days, using three lots of reagents and one instrument.

The results of the lot-to-lot precision study for are shown in the table below:

Test	Samples	N	Mean	Within Lot		Between Lot		Total Precision	
				SD	%CV	SD	%CV	SD	%CV
ALP (U/L)	Control 1	90	74.44	2.10	2.8	0.00	0.0	2.10	2.8
	Control 2	90	165.83	4.86	2.9	0.00	0.0	4.86	2.9
	Sample 1	90	10.24	0.36	3.5	0.17	1.6	0.40	3.9
	Sample 2	90	21.76	0.77	3.5	0.00	0.0	0.77	3.5
	Sample 3	90	46.50	1.16	2.5	0.00	0.0	1.16	2.5
	Sample 4	90	438.24	13.98	3.2	0.00	0.0	13.98	3.2

Test	Samples	N	Mean	Within Lot		Between Lot		Total Precision	
				SD	%CV	SD	%CV	SD	%CV
	Sample 5	90	1112.95	39.67	3.6	0.00	0.0	39.67	3.6
Albumin (g/L)	Control 1	90	37.67	0.41	1.1	0.00	0.0	0.41	1.1
	Control 2	90	53.24	0.55	1.0	0.00	0.0	0.55	1.0
	Low Sample	90	22.07	0.74	3.4	0.00	0.0	0.74	3.4
	Mid Sample	90	43.41	0.74	1.7	0.22	0.5	0.77	1.8
	High Sample	90	53.52	0.41	0.8	0.11	0.2	0.43	0.8

CLSI EP05-A3 was used to evaluate reproducibility of the assay. Using a single lot of reagents and 3 instruments, pooled samples of sera with concentration spanning the analytical measuring range (5 specimens for ALP and 3 specimens for albumin) and 2 controls (Yumizen C1200 N Multi Control and Yumizen C1200 P Multi Control) were tested in duplicate with 2 runs per day over 20 days.

The results of the reproducibility study for are shown in the tables below:

Test	Samples	N	Mean	Repeatability		Between Run		Between Day	
				SD	%CV	SD	%CV	SD	%CV
ALP (U/L)	Control 1	240	81.98	0.65	0.8	2.18	2.7	2.58	3.2
	Control 2	240	201.77	1.03	0.5	4.75	2.4	6.29	3.1
	Sample 1	240	11.71	0.39	3.3	0.36	3.1	0.40	3.4
	Sample 2	240	21.58	0.39	1.8	0.52	2.4	0.71	3.3
	Sample 3	240	56.27	0.56	1.0	2.11	3.7	2.17	3.9
	Sample 4	240	428.89	2.56	0.6	10.79	2.5	15.23	3.6
	Sample 5	240	1,042.42	5.32	0.5	11.10	1.1	13.04	1.3
Albumin (g/L)	Control 1	240	37.8	0.17	0.4	0.90	2.4	0.68	1.8
	Control 2	240	47.1	0.15	0.3	0.38	0.8	0.84	1.8
	Low Sample	240	20.1	0.14	0.7	0.63	3.2	0.17	0.8
	Mid Sample	240	39.3	0.15	0.4	0.55	1.4	0.69	1.8
	High Sample	240	54.2	0.21	0.4	0.71	1.3	0.89	1.6

Test	Samples	N	Mean	Within Lab		Between Lab		Total Precision	
				SD	%CV	SD	%CV	SD	%CV
ALP (U/L)	Control 1	240	81.98	3.44	4.2	3.03	3.7	4.59	5.6
	Control 2	240	201.77	7.95	3.9	6.97	3.5	10.58	5.2
	Sample 1	240	11.71	0.66	5.7	0.52	4.4	0.84	7.2
	Sample 2	240	21.58	0.96	4.4	0.85	4.0	1.29	6.0
	Sample 3	240	56.27	3.08	5.5	2.32	4.1	3.85	6.8
	Sample 4	240	428.89	18.84	4.4	6.92	1.6	20.07	4.7

Test	Samples	N	Mean	Within Lab		Between Lab		Total Precision	
				SD	%CV	SD	%CV	SD	%CV
	Sample 5	240	1,042.42	17.93	1.7	18.21	1.7	25.56	2.5
Albumin (g/L)	Control 1	240	37.8	1.14	3.0	0.10	0.3	1.14	3.0
	Control 2	240	47.1	0.94	2.0	0.00	0.0	0.94	2.0
	Low Sample	240	20.1	0.67	3.3	0.00	0.0	0.67	3.3
	Mid Sample	240	39.3	0.90	2.3	0.12	0.3	0.91	2.3
	High Sample	240	54.2	1.16	2.1	0.00	0.0	1.16	2.1

2. Linearity:

Linearity studies were performed according to CLSI EP06-A guideline. Ten levels of dilutions were prepared by mixing different proportions of serum samples with high and low concentrations of the analytes. Each sample was tested 4 times on a single instrument using a single reagent lot per assay. The summary of the linear regression analysis of the data is presented below:

Test	Slope	Intercept	r^2	Range tested	Claimed Range
ALP	0.9402	3.907	0.993	0-1,620 U/L	6 - 1,200 U/L
Albumin	0.9632	0.4211	0.990	0-60.2 g/L	4.6 - 56 g/L

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

3. Analytical Specificity/Interference:

An interference study was performed based on CLSI EP07-A2 guideline. For both assays (ALP and Albumin) pooled human sera with two different analyte concentrations were spiked with increasing concentrations of the potential interferent and analyzed in quadruplicates. 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 (mg/dL)
ALP	Hemoglobin	500
	Triglycerides	504.88
	Total bilirubin	28.84
	Direct bilirubin	26.36

Analyte	Interferent	Highest concentration tested that did not show significant interference (mg/dL)
	Acetylsalicylic Acid	65.16
	Ascorbic acid	5.98
	Ibuprofen	50.1
	Acetaminophen	20
Albumin	Hemoglobin	375
	Triglycerides	463.75
	Total bilirubin	31.39
	Direct bilirubin	26.27
	Ascorbic acid	5.98
	Ibuprofen	50.10
	Acetaminophen	20
	Acetylsalicylic Acid	65.16

The sponsor includes the following limitation in the labeling of the Yumizen C1200 ALP reagent:
"Measurements in patients treated with asfotase alfa"(Strensiq) are expected to be elevated due to the presence of this drug."

4. Assay Reportable Range:

The claimed measuring ranges are described in the table below.

Analyte	Reportable Range
ALP	6-1,200 U/L
Albumin	4.6 to 56 g/L

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

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

Analyte	Traceability
ALP	IFCC reference measurement procedure
Albumin	ERM-DA470

6. Detection Limit:

Detection capabilities for each analyte were evaluated following the CLSI EP17-A2 guideline.

Limit of blank (LoB) study was performed by testing 1 blank sample of ALP and 4 blank samples of using 2 reagent lots over 4 days on 3 different instruments. Each day, for each reagent lot, 5 replicate measurements were recorded (60 results per reagent lot for ALP and 64 results per reagent lot of albumin). The LoB was calculated non-parametrically at the 95th percentile for each lot. The higher LoB for both reagent lots was chosen as the assay's LoB.

Limit of detection (LoD) study was performed by testing 4 low level samples using 2 reagent lots over 4 days on a single instrument. Each day, for each reagent lot, 4 replicate measurements were recorded (64 results per reagent lot). LoD was calculated non-parametrically. The higher LoD of the two lots was the assay's LoD.

Limit of quantitation (LoQ) study was performed using 4 low level human sera samples measured over 4 days on a single instrument using 2 reagent lots. Each day, for each reagent lot, 4 replicate measurements were recorded (128 results total). The sponsor defines LoQ as the lowest concentration for which the total error (TE) is less than 40%; calculated as |bias|+ 2*standard deviation.

Endpoint	**ALP (U/L)**	**Albumin (g/L)**
LoB	0.71	0.41
LoD	1.40	0.57
LoQ	5.85	3.34
Assay Claimed Range	6 - 1,200	4.6 - 56

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 samples with ALP and albumin analyte concentrations within the claimed analytical ranges of each assay. ALP was measured using the Yumizen C1200 ALP reagent on the Yumizen C1200 analyzer (candidate device) and results were compared to those obtained from the Roche's ALP IFCC Gen.2 assay on the cobas c502 module analyzer (predicate device). Albumin was measured using the Yumizen C1200 Albumin assay on the Yumizen C1200 analyzer and results were compared to those obtained from the ABX PENTRA Albumin CP reagent on the ABX Pentra C400 analyzer (predicate device). Samples were assayed in duplicate over 5 days. Only the first replicate was used for data analysis. The correlation between the predicate device and the candidate are summarized below.

Serum:

Analyte	N	Slope	Intercept	R^2	Test Range	Claimed Measuring Range
ALP	165	0.9402	3.907	0.993	17.8-920.29 U/L	6-1,200 U/L
Albumin	111	0.9632	0.4211	0.990	7.2-54.8 g/L	4.6-56 g/L

Method comparison data supports that serum is an acceptable sample for the ALP and albumin assays.

In addition, the sponsor conducted method comparison studies to demonstrate that the candidate devices can measure ALP and Albumin in lithium heparin plasma samples. Lithium heparin plasma samples were evaluated using the Yumizen C1200 ALP and Yumizen C1200 Albumin reagents on the Yumizen C1200 analyzer and results were compared to those obtained from the predicate devices. Each sample was derived from a single donor in a lithium-heparin collection tube. Each sample was measured by the candidate device in duplicate, but only the first replicate was used for analysis. Results are summarized below:

Analyte	N	Slope	Intercept	R^2	Test Range
ALP	40	1.013	0.3709	0.993	20.39-1,167.67 U/L
Albumin	70	1.009	0.7690	0.988	14.21-55.53 g/L

The results indicate lithium heparin plasma specimens are suitable for use with the candidate devices.

2. Matrix Comparison:

The performance of the device with serum and lithium heparin plasma samples was evaluated in the method comparison section 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:

Reference range studies for the ALP and albumin assays were conducted according to CLSI EP28-A3c to verify values cited from the literature. Serum samples were collected at a blood bank from healthy, normal adults (n=44/sex for ALP and 125 total for albumin).

Each sample was assayed in duplicate. Results of the assays confirm the normal range for adults identified in the literature as referenced below:

ALP

Adults (37°C)[1]

Men:	40-129 U/L
Women:	35-104 U/L

Consensus values (37°C)[2]

Men:	40-130 U/L
Women:	35-105 U/L

Children (37°C)[3]

Boys

0 – 14 days:	83-248 U/L
15 days – < 1 year:	122-469 U/L
1 – < 10 years:	142-335 U/L
10 – < 13 years:	129-417 U/L
13 – < 15 years:	116-468 U/L
15 – < 17 years:	82-331 U/L
17 – < 19 years:	55-149 U/L

Girls

0 – 14 days:	83-248 U/L
15 days – < 1 year:	122-469 U/L
1 – < 10 years:	142-335 U/L
10 – < 13 years:	129-417 U/L
13 – < 15 years:	57-254 U/L
15 – < 17 years:	50-117 U/L
17 – < 19 years:	45-87 U/L

Albumin[4]

4 days - 14 years:	38 - 54 g/L
14 - 18 years:	32 - 45 g/L
20 - 60 years:	35 - 52 g/L
60 - 90 years:	32 - 46 g/L
> 90 years:	29 - 45 g/L

References:

[1] Abicht K, El-Samalouti V, Junge W, et al. Multicenter evaluation of new GGT and ALP reagents with new reference standardization and determination of 37 °C reference intervals. Clin Chem Lab Med 2001;39:Special Supplement pp S 346.

[2] Thomas L, Müller M, Schumann G, et al. Consensus of DGKL and VDGH for interim reference intervals on enzymes in serum. J Lab Med 2005;29:301-308.

[3]Estey MP, Cohen AH, Colantonio DA, et al. CLSI-based transference of the CALIPER database of pediatric reference intervals from Abbott to Beckman, Ortho, Roche and Siemens Clinical Chemistry Assays: Direct validation using reference samples from the CALIPER cohort. Clin Biochem 2013;46:1197–1219.

[4]Roberts WL, McMillin GA, Burtis CA, Bruns DE. Reference Information for the Clinical Laboratory. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th Ed., Burtis CA, Ashwood ER, Bruns DE. (Elsevier Saunders eds. St Louis USA) (2006): 2254.

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.