

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

**A. 510(k) Number:**

k110520

**B. Purpose for Submission:**

To obtain clearance for an automated clinical analyzer with ion selective electrode (ISE) and glucose reagent

**C. Measurand:**

Sodium, potassium, chloride and glucose

**D. Type of Test:**

Quantitative, photometry and potentiometry

**E. Applicant:**

Tokyo Boeki Medisys Inc.

**F. Proprietary and Established Names:**

Biolis 12i

**G. Regulatory Information:**

1. Regulation section:
  - 21 CFR § 862.2160, Discrete photometric chemistry analyzer for clinical use
  - 21 CFR § 862.1665, Sodium test system
  - 21 CFR § 862.1600, Potassium test system
  - 21 CFR § 862.1170, Chloride test system
  - 21 CFR § 862.1345, Glucose test system
2. Classification:

Class I for 21 CFR § 862.2160, Class II for all others
3. Product code:

JJE, JGS, CEM, CGZ, CFR
4. Panel:

75 (Clinical Chemistry)

## **H. Intended Use:**

1. Intended use(s):

See indications for use statements below.

2. Indication(s) for use:

The Biolis 12i Clinical Chemistry analyzer is a discrete photometric chemistry analyzer with ion-selective electrode (ISE), with direct quantitative measurement of sodium, potassium, chloride, and glucose in serum. It is a device intended for the in-vitro, spectrophotometric determination of general chemistry assays for clinical use. The Biolis 12i includes an optional Ion Selective Electrode (ISE) module for the measurement of sodium, potassium and chloride in serum. The Biolis 12i is not for Point-Of-Care testing. It is for vitro diagnostic use only.

Sodium measurements are used in the diagnosis and treatment of diseases involving electrolyte imbalance.

Potassium measurements monitor electrolyte balance and in the diagnosis and treatment of disease conditions characterized by low or high blood potassium levels.

Chloride measurements are used in the diagnosis and treatment of electrolyte and metabolic disorders.

The Biolis 12i analyzer with glucose hexokinase assay is intended to measure glucose quantitatively in human serum. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic glycemia, and of the pancreatic islet cell carcinoma.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Biolis 12i Clinical Chemistry Analyzer

## **I. Device Description:**

The Biolis 12i is an automated clinical analyzer which uses a discrete, single line random access, multiple analysis method. The throughput is 90 tests/hour or 100

tests/hour with ISE synchronization. The system is composed of the sampler, sample delivery, reagent tray, reagent delivery, reaction tray, mixing units, cuvette washing unit, spectrophotometer and other sections.

The Ion-Selective Electrode (ISE) module includes a sodium electrode, a potassium electrode, a chloride electrode, a reference electrode, a cleaning solution and two calibrators (level 1 and 2). The sodium electrode membrane is a crown ether liquid-membrane. The potassium electrode membrane is a valinomycin liquid-membrane. The chloride electrode membrane is a quaternary ammonium salts polymer membrane. The ISE calibrator 1 and 2 contains the following chemicals: sodium, potassium, chloride, sodium formate, triethanolamine,

Glucose reagent kit contains 3x8 mL bottles of R1 reagent. The R1 reagent contains the following: ATP (1.1 mmol/L), NAD (2.7 mmol/L), magnesium (2 mmol/L), hexokinase (yeast) (>2,000 IU/L), G-6-PD (>4,000 IU/L), preservatives and stabilizers.

ISE calibrators have been previously cleared in k050958. Glucose calibrator has been previously cleared in k070202.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

Tokyo Boeki Prestige 24i (ISE)

Beckman CX-7 system (glucose)

2. Predicate K number(s):

k040958, k971467

3. Comparison with predicate:

For ISE:

Similarities and Differences		
Item	Predicate Device (Prestige 24i, k040958)	Candidate Device
Intended Use/Indications for use	Intended to measure the concentration of the electrolytes, sodium, potassium and chloride in serum, using indirect potentiometry. Measurement of sodium,	Same

<b>Similarities and Differences</b>		
<b>Item</b>	<b>Predicate Device (Prestige 24i, k040958)</b>	<b>Candidate Device</b>
	potassium and chloride in serum to is monitor electrolyte balance.	
<b>Instrument</b>	Prestige 24i	Biolis 12i
<b>Instrument throughput and principle</b>	400 tests including ISE Discrete, random access, multi-test analysis	100 tests including ISE Discrete, single-line random access, multi-test analysis
<b>Test Principle</b>	Ion Selective Electrode	Same
<b>Reaction time</b>	Maximum 10 minutes	Same
<b>Analysis time</b>	100 seconds	Same
<b>Measurands</b>	Sodium, Potassium, Chloride	Same
<b>Sample Type</b>	Serum	Same

For glucose:

<b>Item</b>	<b>Predicate device (Beckman CX-7, k971467)</b>	<b>Candidate device</b>
<b>Similarities and Difference</b>		
<b>Intended Use/Indications for use</b>	For quantitative measurements of glucose. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic glycemia, and of the pancreatic islet cell carcinoma.	Same
<b>Measured parameters</b>	glucose	Same
<b>Sample type</b>	Serum	Same
<b>Test principle</b>	hexokinase	Same
<b>Calibrations materials</b>	Aqueous, 2 levels	Aqueous, 1 level

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

None

**L. Test Principle:**

There are two different measuring principles employed, potentiometry and photometry/colorimetry.

Potentiometry: A potential is recorded using a voltmeter, which relates to the concentration of the sample. A reference electrode is used to provide a stable, fixed potential against which other potential differences can be measured. This measurement technique is used for sodium, potassium, and chloride.

Photometry/colorimetry: The change of absorbance measured at 340 nm is monitored for the glucose reaction. The amount of absorbance change is proportional to the concentration of the glucose being present in the sample.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

a. *Precision/Reproducibility:*

Within-run precision for ISE and glucose was determined on a single Biolis 12i using three serum based control materials. 20 replicates of each of the control level were evaluated with the following results:

Analyte	Parameter	Control 1	Control 2	Control 3
Sodium	Mean (mmol/L)	146.7	125.5	138.9
	SD	1.254	0.761	1.298
	%CV	0.85	0.61	0.93
Potassium	Mean (mmol/L)	2.81	5.79	4.20
	SD	0.025	0.053	0.039
	%CV	0.90	0.91	0.94
Chloride	Mean (mmol/L)	105.9	87.6	97.1
	SD	0.841	0.729	0.673
	%CV	0.79	0.83	0.69
Glucose	Mean (mg/dL)	61.9	207.9	364.0
	SD	0.81	2.48	3.80
	%CV	1.31	1.19	1.04

Day-to-day precision for ISE was determined from one run per day for 15 days on a single Biolis 12i. Day to day precision for glucose was determined from 5 different days with runs of five replicates on a single Biolis 12i. Both precision studies used three serum based control materials and results were

summarized below:

Analyte	Parameter	Control 1	Control 2	Control 3
Sodium	Mean (mmol/L)	147.1	125.4	139.5
	SD	0.534	0.518	0.442
	%CV	0.4	0.4	0.3
Potassium	Mean (mmol/L)	2.81	5.79	4.23
	SD	0.023	0.049	0.016
	%CV	0.8	0.9	0.4
Chloride	Mean (mmol/L)	105.9	87.6	97.5
	SD	1.036	0.587	0.385
	%CV	1.0	0.7	0.4
Glucose	Mean (mg/dL)	65.7	221.1	382.2
	SD	0.57	1.73	2.67
	%CV	0.87	0.87	0.70

*b. Linearity/assay reportable range:*

A linearity study for ISE was performed using a high serum sample mixed with a reference solution (with known conc. of NaCl or KCl) to create various target concentrations of analytes. 6 levels of each of the analytes measured were prepared and tested in triplicate on one Biolis 12i analyzer. A linearity study for glucose was performed using commercially available serum linearity standards with target range from 25 to 725 mg/dL. 6 levels of different concentrations of glucose were measured in triplicate on one Biolis 12i analyzer. The observed values were plotted against the expected values and an appropriate line fitted by standard linear regression. Results were summarized below:

	Sodium	Potassium	Chloride	Glucose
Correlation (r)	0.9996	0.9995	0.9984	0.9997
Slope	1.0913	0.9710	0.9667	0.9633
Intercept	- 9.1421	0.1184	6.9739	-2.6641
Range	100-200 (mmol/L)	1-10 (mmol/L)	70-200 (mmol/L)	25-725 (mg/dL)
Levels tested	100, 120, 140, 160, 180, 200 (mmol/L)	1.0, 2.3, 5.0, 7.0, 8.5, 10.0 (mmol/L)	70, 100, 125, 150, 175, 200 (mmol/L)	25, 200, 375, 550, 725 (mg/dL)
% recovery range	96% to 101%	97 to 103%	96 to 101%	100 to 109.3%

Results of the study support the sponsor claims for the following measuring/linearity ranges:

Sodium	Potassium	Chloride	Glucose
100 – 200 mmol/L	1 – 10 mmol/L	70 – 200 mmol/L	25 – 540 mg/dL

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

Traceability:

All the analytes in the calibration solutions are traceable to a reference method and the analyte targets are assigned based on the reference methods or other commercially available methods. See table below for traceability.

Analyte	Traceability
Sodium	Flame photometry
Potassium	Flame photometry
Chloride	Coulometric titration
Glucose	NIST SRM 965b

ISE calibrators- Calibration solutions 1 and 2 had been previously cleared in k040958 (Toyko Boeki Prestige 24i)

Glucose reagents- previously cleared in k971467 (Carolina Liquid Chemistries)

Stability of the ISE calibration solutions: A real-time stability study was performed to demonstrate a maximum shelf life of 18 months at storage temperatures between 15 and 30 degrees C and an open vial stability of 31 days after first opened. Protocols and acceptance criteria has been provided and found to be adequate.

ISE calibrators have been previously cleared in k050958. Glucose calibrator has been previously cleared in k070202.

d. *Detection limit:*

The sponsor determined that the detection limit was defined by the linear range study. The minimum detection limit is defined as the lowest analyte concentrations over the range that the assay has been shown to be acceptably linear by using serum control samples at 6 different concentrations and analyzed by comparing results with the theoretical values. The stated measuring ranges of the candidate device are as follows. These ranges were verified by the linearity study (see section M.1.b. above).

Sodium	Potassium	Chloride
100 – 200 mmol/L	1 – 10 mmol/L	70 – 200 mmol/L

In addition, the sponsor performed a limit of detection study for the glucose

assay according to a modified protocol based on the CLSI EP17-A guideline. LoB was determined by running 5 low samples multiple times on 2 different lots of reagents with one instrument to generate 80 measurements. LoD and LoQ were determined by running 4 low samples four times in two runs with two different lots of reagents on one instrument generating a total of 64 measurements. LoB was calculated to be 2.48 mg/dL and LoD was calculated to be 3.81 mg/dL. LoQ was determined to be 7.83 mg/dL based on inter-assay precision of 9.3%.

The sponsor claimed that the glucose assay has a measuring range of 25 to 540 mg/dL.

*e. Analytical specificity:*

An interference study was conducted to evaluate the potential endogenous and exogenous interfering substances. For endogenous interfering substances, the sponsor tested intralipid, bilirubin, and hemoglobin. For exogenous interfering substances, the sponsor tested lithium, bromide, salicylate, and thiocyanate. Interference studies were performed by spiking serum pool sample at clinically significant medical decision points for each measurand at various concentrations of interfering compounds normally found in serum. Measurements (N=3) obtained from serum containing each potential interfering substance was evaluated and compared against measurements with the unspiked samples. The study was conducted for the analytes Na, K, and CL, and glucose at two analyte concentrations (normal and abnormal). The sponsor states that interferences are considered to be non-significant if the bias between the tested and control samples are within  $\pm 10\%$  for all the analytes.

For endogenous interfering substances, the results demonstrate no significant interference with the sodium, potassium, and chloride when serum contains up to 19.7 mg/dL of unconjugated bilirubin, 21 mg/dL of conjugated bilirubin, 500 mg/dL of intralipid, or 488 mg/dL hemoglobin, however potassium was affected by hemolysis. For glucose, the results demonstrate no significant interference when serum contains up to 20 mg/dL bilirubin, 500 mg/dL hemoglobin, and 1000 mg/dL of Intralipid.

For exogenous interfering substances, the results demonstrate no significant interference with the Na, K, and Cl tests when serum contains up to 3.20 mmol/dL lithium, 37.60 mmol/dL bromide, 4.34 mmol/dL salicylate, and 6.88 mmol/L thiocyanate.

Based on the hemolysis interference, the sponsor has the following limitations in their labeling:



“Do not use hemolyzed samples for potassium since significant hemolysis may increase K concentration because of high levels of K in erythrocytes”.

“Drugs and other substances may affect sodium, potassium, chloride, and glucose determinations. See Young, D.S.<sup>1</sup> for a compilation of reported interferences”

1. Young, D.S., Effects of Drugs on Clinical Laboratory Tests, third edition, AACC Press, Washington D.C., 1990.

f. *Assay cut-off:*

Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

i.) For ISE method comparison study:

A total of 140 patient serum samples were assayed on one Biolis 12i (candidate device) and one Prestige 24i (predicate device) analyzer at Tokyo Boeki Medical System’s laboratory. Some samples were diluted and spiked to cover the hard-to-find sample range (no more than 20%). The linear regression results are as follows:

*Sodium:*

Correlation Coefficient	0.9872
Slope	1.0204
Intercept	-3.1903
Sample range tested	100 – 195.9 mmol/L

*Potassium:*

Correlation Coefficient	0.9992
Slope	1.0255
Intercept	-0.1457
Sample range tested	1.0 – 10.0 mmol/L

*Chloride:*

Correlation Coefficient	0.9922
Slope	0.9736
Intercept	1.8580
Sample range tested	70 - 200 mmol/L

ii.) For glucose method comparison study:

A total of 124 patient serum samples were evaluated using the candidate device (Biolis 12i) and the predicate device (Beckman CX7). Some samples were spiked and diluted to obtain the hard-to-find sample range (13%). The linear regression results were summarized below:

*Glucose:*

Correlation Coefficient	0.997
Slope	1.045
Intercept	-4.858
Sample range tested	29-540 mg/dL

b. *Matrix comparison:*

Not applicable.

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 values may vary with age, sex, diet, geographic location and instrumentation. Good laboratory practice dictates that each laboratory establishes its own expected values to reflect its patient population. Suggested guidelines are as follows:

*Sodium:*

Adult: 136 – 145 mmol/L

Kathleen Deska Pagana and Timothy James Pagana, Mosby's Diagnostic and Laboratory Test Reference, 2nd ed. (St. Louis: Mosby, 1995), p 744.

*Potassium:*

Adult: 3.5 – 5.0 mmol/L

Kathleen Deska Pagana and Timothy James Pagana, Mosby's Diagnostic and Laboratory Test Reference, 2nd ed. (St. Louis: Mosby, 1995), p 638.

*Chloride:*

Adult/elderly: 90 – 110 mmol/L

Kathleen Deska Pagana and Timothy James Pagana, Mosby's Diagnostic and Laboratory Test Reference, 2nd ed. (St. Louis: Mosby, 1995), p 197.

*Glucose:* 70-105 mg/dL

Tietz, N. W., Clinical Guide to Laboratory Tests, W.B. Saunders Co., Philadelphia, PA, 1983.

**N. Instrument Name:**

Biolis 12i

**O. System Descriptions:**

1. Modes of Operation:

Single sample

2. Software:

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

Yes  or No

3. Specimen Identification:

Manual sample identification or Barcode reader

4. Specimen Sampling and Handling:

Automatic sample aspiration: samples need to be pour over into a sample cup and put onto the sample tray.

5. Calibration:

Operator must initiate a calibration sequence of the calibration solutions (2 levels) at the start of the morning and every 24 hours subsequently.

6. Quality Control:

Control materials are supplied by Mircrogenics, Chem Trak H, 3 levels of serum based liquid controls (k030942).

Operator must initiate an external quality control procedure the quality control materials. Recommendations for frequency of testing are including in the labeling. As a minimum, users are to follow regulatory guidelines for testing quality control materials.

**P. ~~Other Supportive Instrument Performance Characteristics Data Not Covered In~~ The “Performance Characteristics” Section above:**

To assess the effect of temperature on test results across the recommended range of ambient temperature (15 – 30°C), the sponsor conducted an ambient temperature study using 30 native patient samples. Calibrations were performed at each of these temperatures (15 °C, 23 °C, and 30°C) and testing was performed at all the three temperatures for each calibration temperature. Protocols and acceptance criteria provided are found to be adequate. Based on the ambient temperature study, the sponsor claimed that ambient temperature between 15 - 30°C will not affect the performance of the device.

**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.