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

A. 510(k) Number:

k140373

B. Purpose for Submission:

The cobas 8000 ISE module and the ISE Gen 2 reagents were previously cleared for serum and plasma sample types under k100853 and urine was added as a sample type in k123726. In this submission, the measurement of urine has been modified to (1) add a measuring range extension below the standard measuring range (Under Range Rerun) and (2) to include a new LHH calibration scheme (Low/High/High) in which all three standards (S1, S2 and S3) are used for the full calibration with S3 used as a compensator. The LHH calibration scheme applies to the standard measuring range and extended measuring range.

C. Measurand:

Sodium, potassium, and chloride

D. Type of Test:

Quantitative, indirect potentiometric measurement with ion-selective electrodes

E. Applicant:

Roche Diagnostics

F. Proprietary and Established Names:

cobas 8000 ISE Indirect Na, K, Cl for Gen 2.

G. Regulatory Information:

Panel	Product Code	Class	Classification Name	Regulation
Clinical Chemistry (75)	JGS	II	Ion Specific Electrode, Sodium	21 CFR 862.1665
Clinical Chemistry (75)	CEM	II	Ion Specific Electrode, Potassium	21 CFR 862.1600
Clinical Chemistry (75)	CGZ	II	Ion Specific Electrode, Chloride	21 CFR 862.1170

H. Intended Use:

1. Intended use(s):

   See Indication(s) for use below.

2. Indication(s) for use:

   The cobas 8000 ISE module is a fully automated ion-specific analyzer intended for the *in vitro* potentiometric determination of chloride, potassium, and sodium in serum, plasma, and urine using ion-selective electrodes. Measurements obtained by this device are used in the diagnosis and treatment of diseases or conditions involving electrolyte imbalance.

3. Special conditions for use statement(s):

   For *in vitro* diagnostic use only.

   For prescription use.

4. Special instrument requirements:

   cobas 8000 ISE Modular Analyzer

I. Device Description:

The cobas 8000 ISE module is an Ion-Selective Electrode (ISE) system for the determination of sodium, potassium, and chloride in serum, plasma, and urine. The ISE module includes a sodium electrode, a chloride electrode, a potassium electrode, a reference electrode, an ISE calibrator and an ISE Compensator.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   cobas 8000 ISE Indirect Na, K, Cl for Gen. 2

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

   k123726

3. Comparison with predicate:

   The following tables compare the cobas 8000 ISE module and its predicate device, the cobas 8000 ISE Module cleared under k123726.

Similarities		
Parameter	**cobas 8000 Urine ISE (k123726)**	**cobas 8000 Urine ISE (k140373)**
Intended Use	The cobas 8000 ISE module is intended for the	Same

	quantitative determination of chloride, potassium, and sodium in serum, plasma, and urine using ion-selective electrodes.	
Measurement principle	ISE Potentiometry	Same
Ion selective electrodes (ISE)	Potentiometric chloride, potassium, sodium and reference electrodes	Same
Reportable range for urine	60-350 mmol/L (Sodium and Chloride) 3-100 mmol/L (Potassium)	Same

Differences		
Parameter	**Predicate device (k123726)**	**Candidate device (k140373)**
Extended Range	No Extended Range	20-59.9 mmol/L via Under Range application for Sodium and Chloride
Calibration scheme	L/H/Sc (Low/High/Serum compensator)	LHH (Low/High/High)

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

CLSI EP5-A2: Evaluation of Precision of Clinical Chemistry Devices.

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.

L. Test Principle:

Sodium, potassium and chloride are measured using ion-selective electrodes utilizing an indirect (diluted) method where urine samples are automatically diluted at 1:46 ratio (standard range) or 1:31 (under range) using ISE diluent. Each of the electrodes (Sodium, Potassium and Chloride) has a membrane with an open liquid junction that is ion-selective. The reference electrode uses the same design of the ion-electrodes and it is exclusively used as a reference for every measurement. The difference of all voltages between the reference electrode and any ion-selective electrode is a measure for the concentration of individual ions. For every test, the voltages of both ISE internal standard and diluted sample solution are measured for each type of ions (Sodium, Potassium and Chloride). The measurement of

all electrodes is performed in parallel. The resulting voltages are converted into operator readable results.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision studies for the cobas 8000 ISE electrodes for the measurement of Na, K, and Cl using the LHH calibration scheme were performed using one analyzer, one site, one lot of reagent, and six samples. The six samples used for the precision testing were comprised of four human urine sample pools (HU) of varying concentrations (low, mid, Medical Decision Level (MDL), and high) for each analyte; and Liquichek Level 1 and Liquichek Level 2 controls. Separate studies were conducted for the normal (standard) assay measuring range (sample volume 10 µl) and the automatic rerun using increased sample volume (15 µl).

The within run precision study was performed with 21 single determinations for each analyte. The intermediate precision was performed over a period of 21 days, two runs per day, and two aliquots per run for a total of 84 samples per analyte. The summaries for the precision studies are presented in the tables below:

Within Run Precision

Sodium (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	83.4	175.6	69.9	174.5	347.2
SD	0.3	1.3	0.2	0.5	0.9
%CV	0.3	0.8	0.3	0.3	0.3

Potassium (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	30.64	66.22	3.47	50.7	93.48
SD	0.2	0.61	0.01	0.26	0.58
%CV	0.6	0.9	0.3	0.5	0.6

Chloride (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	97.5	193.2	65.3	167.6	333.5
SD	0.9	2.0	0.9	1.1	3.5
%CV	0.9	1.0	1.3	0.7	1.0

Sodium Rerun, 20.0-59.9 mmol/L (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU MDL	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21	21
Mean	42.1	32.2	24.7	37.7	31.7	56.8
SD	0.3	0.3	0.2	0.2	0.2	0.4
%CV	0.6	0.8	0.9	0.6	0.7	0.6

Chloride Rerun, 20.0-59.9 mmol/L (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU MDL	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21	21
Mean	43.7	29.0	21.6	34.2	28.0	55.0
SD	0.3	0.4	0.2	0.3	0.2	0.4
%CV	0.7	1.5	1.0	0.9	0.9	0.8

Total (Intermediate) Precision

Sodium (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	83.4	175.6	69.9	174.5	347.2
SD	1.3	1.7	1.3	1.1	2.8
%CV	1.6	1.0	1.8	0.7	0.8

Potassium (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	30.64	66.22	3.47	50.7	93.48
SD	0.32	1.14	0.04	0.63	1.82
%CV	1.0	1.7	1.1	1.2	1.9

Chloride (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21
Mean	97.5	193.2	65.3	167.6	333.5
SD	0.9	2.0	0.9	1.1	3.5
%CV	0.9	1.0	1.3	0.7	1.0

Sodium Rerun, 20.0-59.9 mmol/L (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU MDL	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21	21
Mean	42.1	32.2	24.7	37.7	31.7	56.8
SD	1.0	1.0	0.9	1.0	1.0	1.1
%CV	2.5	3.9	3.7	2.7	3.0	1.9

Chloride Rerun, 20.0-59.9 mmol/L (Urine)

Sample	Liq 1	Liq 2	HU low	HU med	HU MDL	HU high
Unit	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
n	21	21	21	21	21	21
Mean	43.7	29.0	21.6	34.2	28.0	55.0
SD	1.0	0.9	0.8	0.9	0.8	0.9
%CV	2.3	3.2	3.7	2.5	3.0	1.7

b. Linearity/assay reportable range:

The measuring range is 60-350 mmol/L for sodium and chloride in urine on the cobas 8000 ISE module (standard range). The sponsor has added an automatic rerun function for measurement of the sodium and chloride in urine in the low range (Under Range) of 20-59.9 mmol/L.

The Under Range rerun is triggered automatically when the initial sample result is measured below the standard measuring range for sodium and/or chloride samples (below 60 mmol/L). A rerun order is automatically generated by the software and a new sample is measured using an increased sample volume of 15 µl instead of the standard 10 µl (sample dilution ratio of 1:31 vs. 1:46, respectively) to rerun the patient sample. The current measuring range for potassium in urine is 3-100 mmol/L and this range is not being expanded.

Linearity studies were performed according to CLSI EP6-A for the automatic rerun function. A dilution series of eleven concentrations was prepared using urine sample

pools for each of the analytes and tested in triplicate. Linear regression analysis was done according to EP6-A. Linear regression summary results are presented in the table below:

Linearity Analysis for Automatic Rerun

Analyte	Slope	Intercept	Concentration range of samples tested (mmol/L)
Sodium	0.9834	1.385	18.1 to 61.8
Chloride	1.0189	-0.5900	16.5 to 60.1

Additional linearity studies were performed for the standard measuring range with LHH calibration scheme. Linear regression summary results are presented in the table below:

Linearity Analysis for Standard Measuring Range

Analyte	Slope	Intercept	Concentration range of samples tested (mmol/L)
Sodium	1.0214	-2.8874	60.0 to 350.0
Potassium	1.0274	-0.031	3.0 to 110.0
Chloride	1.0024	-7.0149	60.0 to 350.0

Linearity studies using the LHH calibration scheme support the sponsor's claimed measuring ranges for urine samples of 60-350 mmol/L (sodium and chloride) and 3-100 mmol/L (potassium) and the extended ranges of 20-59.9 mmol/L for sodium and chloride.

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

The ISE Calibrators ISE Standard Low (S1) and ISE Standard High (S2 and S3) are standardized against primary calibrators prepared gravimetrically from purified salts. The calibrators were cleared in k132418. The LHH calibration scheme is being implemented for the cobas 8000 in this submission.

d. *Detection limit:*

Studies were carried out in accordance with CLSI Guidance Document EP17-A for sodium and chloride for the automatic rerun using increased sample volume. For determination of LoB, one analyte free sample was measured in five replicates, six runs, three days, on two cobas 8000 ISE modules. A total of 60 measurements were obtained per analyzer. For determination of LoD, five samples (one replicate) with low-analyte concentration were measured in six runs for three days on two cobas 8000 ISE modules. In total 60 measurements were obtained per analyzer. For LoQ studies, a low level sample set was prepared by diluting three human urine samples with an analyte free diluent (ISE Diluent). The low level sample set was tested in single replicate for three days in two runs per day on two cobas 8000 ISE modules.

LoQ is defined as the concentration where total error is less than 30%. Results from the detection limit studies for the automatic rerun function are summarized in the table below:

Analytes	LoB (mmol/L)	LoD (mmol/L)	LoQ (mmol/L)	Claimed Measuring Range (mmol/L)
Sodium	6.9	9.3	12.6	20.0 to 59.9
Chloride	6.3	7.4	9.8	20.0 to 59.9

For detection limit studies for potassium, the rerun function is not implemented. Therefore, a verification of the LoQ of the cobas 8000 ISE module was conducted for potassium. A low level sample set was prepared by diluting 3 human urine samples with an analyte free diluent (ISE Diluent). The low level sample set was tested in single replicate for three days in two runs per day on two cobas 8000 ISE modules. LoQ is defined by the sponsor as the concentration where total error is less than 30%. Results from the detection limit study are summarized in the table below:

Analyte	LoQ (mmol/L)	Claimed Measuring Range (mmol/L)
Potassium	1.13	3.0 to 100.0

Additional detection limit studies were performed to demonstrate that the LoB, LoD and LoQ for the standard range for sodium, potassium and chloride have not changed due to the proposed new LHH calibration method. Results from the detection limit study are summarized in the table below:

Analytes	LoB (mmol/L)	LoD (mmol/L)	LoQ (mmol/L)	Claimed Measuring Range (mmol/L)
Sodium	8.1	9.8	15.51	60.0 to 350
Chloride	7.8	9.0	18.34	60.0 to 350
Potassium	0.28	0.35	1.13	3.0 to 100.0

e. *Analytical specificity:*

Interference testing was conducted for the automatic rerun using increased sample volume. Urine sample pools with known concentrations of each analyte were spiked with drugs and concentrations listed below. The analyte concentrations of the spiked aliquots were tested in triplicate and the mean of the triplicate determinations is compared to the analyte concentration of the reference sample which contains no drugs. The known concentration of the urine pools were 32.5 mmol/L for sodium and 27.6 mmol/L for chloride. Additionally, hemoglobin interference was tested by spiking a human urine sample (containing sodium and chloride at 22.1 mmol/L) with several concentrations of hemoglobin (105 to 1050 mg/dL). Conjugated bilirubin interference was tested by spiking a human urine sample (containing sodium at 43.5 mmol/L and chloride at 45.5 mmol/L) with several concentrations of conjugated bilirubin (1.0 to 66.0 mg/dL). Significant interference is defined by the sponsor as

recovery ≥ ±10% of the initial value. There was no significant interference for urine sodium or chloride when these analytes and interferents were tested at the concentrations indicated below.

Drug	Highest concentration at which no significant interference
Acetaminophen	3000
N-Acetyl cysteine	10
Salicyluric acid	6000
Ascorbic acid	4000
Na-Cefoxitin	12000
Gentamycin Sulfate	400
Ibuprofen	4000
Levodopa	1000
Methyldopa	2000
Ofloxacine	900
Phenazopyridine	300
Tetracycline (Doxycycline)	300
Hemoglobin	1000
Conjugated bilirubin	66

Evaluation of pH interference was conducted for the automatic rerun for sodium and chloride using urine samples (containing sodium at 34.7 mmol/L and chloride at 31.4 mmol/L) adjusted at pH values ranging from 3.7 to 8.7. There was no significant interference for sodium and chloride at pH range 3.7 to 8.7.

The above interference data obtained for the under range re-run function are consistent with the interference studies performed for the standard range function for sodium, potassium and chloride in k123726.

Interference data were provided for the ISE electrodes using the LHH function under k132418.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Sodium, potassium, and chloride values for urine samples were obtained on the cobas 8000 ISE module using the LHH calibration scheme and were compared to those determined on the corresponding reference method and to the predicate cobas 8000 ISE with the L/H/Sc calibration scheme. The reference methods used were: Flame

Photometer IL 943 for sodium/potassium and coulometric (Chloride Analyzer 926S) for chloride. No more than 20% of the samples were either spiked or diluted to cover the measuring range. Samples in the normal assay range were run on the cobas 8000 ISE module using the LHH calibration method and compared to samples on the same analyzer using the existing L/H/Sc calibration method for the cobas 8000 ISE module. In addition, samples were tested in singlicate on one cobas 8000 ISE and were compared with the cobas c501 for the automatic rerun of sodium and chloride samples in the range of 20.0-59.9 mmol/L. The cobas c501 (k132418) was used as a comparator for the low range for sodium and chloride in addition to the Flame Photometer and Chloride Analyzer because it has the ability to measure in this range (20-250 mmol/L). The results were calculated using Passing/Bablok Linear regression. The method comparison result summary is shown in the tables below:

Sodium Method Comparison
Flame photometer vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
106	69.2 to 337.4	y = 0.997x + 0.984	0.9995

Sodium Method Comparison
cobas 8000, existing L/H/Sc calibration method vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	65.3 to 342.1	y = 1.021x - 4.562	0.9999

Potassium Method Comparison
Flame photometer vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
99	3.80 to 86.30	y = 1.014x + 0.507	0.9997

Potassium Method Comparison
cobas 8000, existing L/H/Sc calibration method vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	4.87 to 96.94	y = 1.021x - 0.208	0.9998

Chloride Method Comparison
Coulometer vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
100	66.0 to 287.0	y = 1.029x - 3.996	0.9995

Chloride Method Comparison
cobas 8000, existing L/H/Sc calibration method vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	62.2 to 330.5	y = 1.023x - 3.284	0.9998

Automatic Rerun Sodium Method Comparison
flame photometer vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	22.2 to 58.7	y = 0.943x + 3.149	0.9991

Automatic Rerun Sodium Method Comparison
cobas c501 vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	24.2 to 59.8	y = 0.962x + 1.11	0.9995

Automatic Rerun Chloride Method Comparison
coulometer vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	22.0 to 59.0	y = 0.973x - 0.927	0.9987

Automatic Rerun Chloride Method Comparison
cobas c501 vs. cobas 8000, new L/H/H calibration method

n	Range (mmol/L)	Regression Passing-Bablok	r
92	20.2 to 57.3	y = 0.981x + 0.728	0.9992

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:

   The expected values for adult based on 24-hour urine output are cited from the literature [1] in the labeling:

   Sodium: 40 to 220 mmol/24h
   Potassium: 25 to 125 mmol/24h
   Chloride: 110 to 250 mmol/24h

   [1] Tietz Fundamentals of Clinical Chemistry, Fifth Edition, Edited by Carl A. Burlis and Edward R. Ashwood, W.B. Saunders Company, 2001:970, 1004,1009 (ISBN 0-7216-8634-6.

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.