February 12, 2026

Roche Diagnostics
Noel Mencias
Senior Regulatory Affairs Manager
9115 Hague Rd.
Indianapolos, Indiana 46250

Re: K253491
Trade/Device Name: ISE indirect K for Gen. 2; ISE indirect Na for Gen. 2; ISE indirect Cl for Gen. 2; cobas pro integrated solutions
Regulation Number: 21 CFR 862.1600
Regulation Name: Potassium test system
Regulatory Class: Class II
Product Code: CEM, JGS, CGZ, JJE
Dated: November 14, 2025
Received: November 14, 2025

Dear Noel Mencias:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality Management System Regulation (QMSR) (21 CFR Part 820), which includes, but is not limited to, ISO 13485 clause 7.3 (Design controls), ISO 13484 clause 8.3 (Nonconforming product), and ISO 13485 clause 8.5 (Corrective and preventative action). Please note that regardless of whether a change requires premarket review, the QMSR requires device manufacturers to review and approve changes to device design and production (ISO 13485 clause 7.3 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the Quality Management System Regulation (QMSR) (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-

assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

THOMAS C. MILLER -S Date: 2026.02.12 17:30:20 -05'00'

for Paula Caposino, Ph.D.
Deputy Director
Division of Chemistry
and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K253491

Device Name
cobas pro integrated solutions;
ISE indirect Na for Gen.2; ISE indirect K for Gen.2; ISE indirect Cl for Gen.2

Indications for Use *(Describe)*
cobas pro integrated solutions is an automated analyzer, intended for running qualitative, semiquantitative, and quantitative clinical chemistry and immunochemistry assays as well as ion-selective measurements.

The ISE analytical unit of the cobas c systems is intended for the quantitative determination of sodium, potassium and chloride in serum, plasma or urine using ion-selective electrodes.

Sodium measurements are used in the diagnosis and treatment of aldosteronism (excessive secretion of the hormone aldosterone), diabetes insipidus (chronic excretion of large amounts of dilute urine, accompanied by extreme thirst), adrenal hypertension, Addison's disease (caused by destruction of the adrenal glands), dehydration, inappropriate antidiuretic hormone secretion, or other diseases involving electrolyte imbalance.

Potassium measurements are used to monitor electrolyte balance 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 such as cystic fibrosis and diabetic acidosis.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

cobas pro integrated solutions; ISE indirect Na for Gen.2; ISE indirect K for Gen.2; ISE indirect Cl for Gen.2 (K253491)

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Noel Mencias Phone: (463) 336-2546 Email: noel.mencias@roche.com
Date Prepared	October 24, 2025
Proprietary Name	ISE indirect K for Gen.2 ISE indirect Na for Gen.2 ISE indirect Cl for Gen.2 **cobas pro** integrated solutions
Common Name	ISE indirect K for Gen.2 ISE indirect Na for Gen.2 ISE indirect Cl for Gen.2 **cobas pro** integrated solutions
Classification Name	Electrode, Ion-Specific, Potassium Electrode, Ion-Specific, Sodium Electrode, Ion-Specific, Chloride Analyzer, chemistry (photometric, discrete), for clinical Multi-Analyte
Product Codes, Regulation Numbers	CEM, 21 CFR 862.1600 JGS, 21 CFR 862.1665 CGZ, 21 CFR 862.1170 JJE, 21 CFR 862.2160
Predicate Devices	**cobas** 6000 Series System **cobas pro** integrated solutions ISE indirect K for Gen.2 ISE indirect Na for Gen.2 ISE indirect Cl for Gen.2
Establishment Registration	Roche Diagnostics GmbH Mannheim, Germany: 9610126 Roche Diagnostics GmbH Penzberg, Germany: 9610529 Roche Diagnostics Indianapolis, IN United States: 1823260

1. DEVICE DESCRIPTION

cobas pro integrated solutions is an automated analyzer, intended for running qualitative, semiquantitative, and quantitative clinical chemistry and immunochemistry assays as well as ion-selective measurements.

An Ion-Selective Electrode (ISE) makes use of the unique properties of ion-selective membrane to develop an electrical potential (electromotive force, EMF) for the measurements of ions in solution. Selective membrane is in contact with both the test solution and an internal filling solution. Due to the selectivity of the membrane, only the ions to be measured contribute to the EMF. The membrane EMF is determined by the difference in concentration of the test ion in the test solution and the internal filling solution.

Electrolytes are involved in most major metabolic functions in the body. Sodium and potassium are amongst the most important physiological ions and the most often assayed electrolytes. They are supplied primarily through the diet, absorbed in the gastrointestinal tract, and excreted via the kidneys.

Sodium is the major extracellular cation and functions to maintain fluid distribution and osmotic pressure. Some causes of decreased levels of sodium include prolonged vomiting or diarrhea, diminished reabsorption in the kidney and excessive fluid retention. Common causes of increased sodium include excessive fluid loss, high salt intake and increased kidney reabsorption.

Potassium is the major intracellular cation and is critical to neural and muscle cell activity. Some causes of decreased potassium levels include reduced intake of dietary potassium or excessive loss of potassium from the body due to diarrhea, prolonged vomiting or increased renal excretion. Increased potassium levels may be caused by dehydration or shock, severe burns, diabetic ketoacidosis, and retention of potassium by the kidney.

Chloride is the major extracellular anion. Similarly to the other ions, common causes of decreased chloride include reduced dietary intake, prolonged vomiting and reduced renal reabsorption as well as some forms of acidosis and alkalosis. Increased chloride values are found in dehydration, kidney failure, some forms of acidosis, high dietary or parenteral chloride intake, and salicylate poisoning.

2. INDICATIONS FOR USE

cobas pro integrated solutions is an automated analyzer, intended for running qualitative, semiquantitative, and quantitative clinical chemistry and immunochemistry assays as well as ion-selective measurements.

The ISE analytical unit of the **cobas c** systems is intended for the quantitative determination of sodium, potassium and chloride in serum, plasma or urine using ion-selective electrodes.

Sodium measurements are used in the diagnosis and treatment of aldosteronism (excessive secretion of the hormone aldosterone), diabetes insipidus (chronic excretion of large amounts of dilute urine, accompanied by extreme thirst), adrenal hypertension, Addison's disease (caused by destruction of the adrenal glands), dehydration, inappropriate antidiuretic hormone secretion, or other diseases involving electrolyte imbalance.

Potassium measurements are used to monitor electrolyte balance 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 such as cystic fibrosis and diabetic acidosis.

3. TECHNOLOGICAL CHARACTERISTICS

The following table compares the **cobas** ISE neo versus the **cobas 6000** (**cobas c** 501 with integrated ISE).

Table 1: cobas ISE neo Technological Characteristics

	Predicate **cobas c 501 (K060373)**	**Candidate** **cobas ISE neo (K253491)**
Intended Use	The ISE module of Roche/Hitachi **cobas c** systems intended for the quantitative determination of sodium, potassium, and chloride in serum, plasma, or urine using ion-selective electrodes.	The ISE analytical unit of the **cobas c** systems is intended for the quantitative determination of sodium, potassium, and chloride in serum, plasma or urine using ion-selective electrodes.

	Predicate **cobas c 501 (K060373)**	**Candidate** **cobas ISE neo (K253491)**
Measurement Principal	ISE Potentiometry	Same
Throughput	600 tests/hr	900 tests/hr
Analyzer Configuration	Single module integrated in analyzer c module	Self-contained, does not share infrastructure with other analzyers.
Sample Handling		
Typical Sample Volumes	9.7 µL	15 µL
Default ISE Dilution ratio	1:31	Same
Diluent	ISE Diluent Gen.2	System water
Sample Types	Serum, plasma, urine	Same
Sample handling system	Input of samples via core input buffer using universal sample racks	Same
Sample Identification	Barcode on the sample or position on the rack	Same
Reagent Handling		
Reagent container (electrolytes)	600 mL bottles for ISE Internal Standard (IS), 300 mL bottles for ISE Diluent and ISE Reference Electrolyte	510 mL bottles with screwcap and straw for concentrated ISE Internal Standard (IS). 2000 mL bottle for ISE Reference Electrolyte
Reagent Access	Pipettor	via Reagent sipper
Onboard Storage Temperature	Ambient temperature	Same
Reagent bottle/Cassette identification	Barcode	RFID
On board reagent storage capacity	2x600mL ISE Diluent, 2x300mL Diluent, 1x300mL ISE Reference Electrolyte.	1x510mL IS Gen.2 concentrated 1x2000mL ISE Reference Electrolyte
ISE cycle time	18 seconds	12 seconds
Sample mixing	photometric cuvette	in ISE Dilution vessel
Automatic Rerun	Available	Same
Application information transfer to instrument	Hard coded application information	Parameterized application information.
Auxiliary Reagents	Activator for **cobas** Systems, ISE Cleaning solution	Same
Pipetting System		
Sample and Reagent Syringes	XY robotic	Same

	Predicate **cobas c 501 (K060373)**	**Candidate** **cobas ISE neo (K253491)**
Sample probes	One polished steel probe	Same
Probe Cleaning	Automatic for all probes	Same
Liquid Level Detection	Available for sample pipetting	Same
Clot Detection	Provided	Same
Supply of degassed water	The ISE measurement unit receives degassed water from the **cobas c** module	The ISE measuring units receive degassed water from its own water supply
Test Reaction Chamber		
Measurement Temperature	37°C	Same
Control Systems	Temperature adjustment/monitoring are managed by the adjacent **cobas c** module	Temperature adjustment/ monitoring are managed by the **cobas** ISE neo itself (self contained)
Supply of vacuum	The ISE measuring unit is supplied for vacuum by the adjacent **cobas c** module	The ISE measurement unit is supplied for vacuum by the **cobas** ISE neo itself (self-contained)
ISE Unit		
ISE unit	Module permanently connected via shared infrastructural elements to clin chem analyzers	Same
ISE measurement unit	Hold Na, K, Cl, and Ref-Electrode, and required tubing etc.	Same
Dilution Sample/ISE Diluent	Performed in cuvettes of the clinical chemistry analytical unit	Performed in an ISE dilution vessel
Calibration and Quality Control		
Calibrators	ISE Standard Low/High	Same
Calibrator Set points	Na: 160/120 mmol/L K: 7.0/3.0 mmol/L Cl: 120/80 mmol/L	Same
Calibration Modes	Linear (Two point, Slope)	Linear (Two point, Slope); optional Automatic Calibration
Calibration Stability	24 h	Same
On-board QC	Not Available	Optional
On line QC	Yes	Same
Control storage on instrument	In remote buffer at ambient temperature	Same
Calibrator/control value transfer	Via remote transfer or CD	Same

	Predicate **cobas c 501 (K060373)**	**Candidate** **cobas ISE neo (K253491)**
Compensation scheme	Low High High (LHH)	Same
Internal quality management system	Available to monitor and validate test results	Same
Interfaces		
Tubing	No branching (sample) flow path	Same
Printer	Laser	Same
Display	Touch screen without physical keyboard and mouse	Same
Reagents		
Internal Standard (IS)	ISE Internal Standard Gen.2	31x Concentrated Internal Standard (IS) – diluted on-board to equivalent concentration
Diluent	ISE Diluent Gen.2	System Water
Cleaning Solution	ISE Cleaning Solution	Same
Deproteinizer	Not Available	ISE Deproteinizer
Calibrator	ISE Standard Low ISE Standard High	Same
Control	Precinorm U Plus Precipath U Plus PreciControl ClinChem Multi 1 PreciControl ClinChem Multi 2	PreciControl ClinChem Multi 1 PreciControl ClinChem Multi 2
Software		
Software	**cobas 6000** system software	**cobas pro** integrated solutions system software
Configuration	One or several analytical units with one PC and one core	One ISE analytical unit per core
Units Controlled	Depending on configuration	Same
Function performed	Data Input, sample processing, result calculation, result reporting, quality control	Same
PC (Control Unit) Functions	Data input (keyboard, disc) data output (screen, printer, host)	Same
Core Unit Functions	Real time database, data input and output (via HOST communication), control of sample conveyer	**cobas pro** core with real time database, data input and output (via system software communication), control of sample conveyer
Analytical Unit(s) Functions	Control of analytic processes (pipetting, incubation,	Same

	Predicate cobas c 501 (K060373)	Candidate cobas ISE neo (K253491)
	detection) Primary Signal processing	
MSB Functions	Intermediate storage of sample racks	Same
Data Storage	Real time database in Core Unit (storage of System and Application parameters, Calibration Data, QC Data, Sample results, Alarm History)	Same
Software Controlled test countdown	Available	Same
Result Calculation	Automated measuring of signal for kinetic and endpoint methods according to cycle time and automated calculation of concentrations via calibration curve	Same
Flagging of Errors	Available	Same
Controls (e.g. Power, pressure, temperature)	Available	Same (location changed, but not devices/function)

Table 2: Similarities and Differences between the ISE indirect Na for Gen.2 on the cobas pro ISE versus the cobas ISE neo

	Predicate ISE indirect Na for Gen.2 on cobas pro ISE (K191899)	Candidate ISE indirect Na for Gen.2 on cobas ISE neo (K253491)
Proprietary name	ISE indirect Na for Gen.2	Same
Intended use	The ISE analytical unit of the Roche/Hitachi **cobas c** systems is intended for the quantitative determination of sodium in serum, plasma or urine using ion-selective electrodes.	The ISE analytical unit of the **cobas c** systems is intended for the quantitative determination of sodium in serum, plasma or urine using ion-selective electrodes.
Technology	ISE Potentiometry	Same
Test type	Quantitative	Same
Default sample volumes	15 µL	Same
Default ISE Dilution ratio	1:31	Same
Sample types	Serum, plasma, urine	Same
Sample handling system	Input of samples via core input buffer using universal sample	Same

	Predicate ISE indirect Na for Gen.2 on cobas pro ISE (K191899)	Candidate ISE indirect Na for Gen.2 on cobas ISE neo (K253491)
	racks	
Sample Identification	Barcode	Same
Measuring Range	Serum/Plasma: 80-180 mmol/L Urine: 20-250 mmol/L	Same

Table 3: Similarities and Differences between the ISE indirect K for Gen.2 on the cobas c 501 ISE ISE versus the cobas ISE neo

	Predicate ISE indirect K for Gen.2 on cobas c 501 (K060373)	Candidate ISE indirect K for Gen.2 on cobas ISE neo (K253491)
Proprietary name	ISE indirect K for Gen.2	Same
Intended use	The ISE analytical unit of the Roche/Hitachi **cobas c** systems is intended for the quantitative determination of potassium in serum, plasma or urine using ion-selective electrodes.	The ISE analytical unit of the **cobas c** systems is intended for the quantitative determination of potassium in serum, plasma or urine using ion-selective electrodes.
Technology	ISE Potentiometry	Same
Test type	Quantitative	Same
Typical sample volumes	9.7 µL	15 µL
Default ISE Dilution ratio	1:31	Same
Sample handling system	Input of samples via core input buffer using universal sample racks	Same
Sample Identification	Barcode	Same
Measuring Range	Serum/Plasma: 1.5-10.0 mmol/L Urine: 3-100 mmol/L	Same

Table 4: Similarities and Differences between the ISE indirect Cl for Gen.2 on the cobas c 501 ISE versus the cobas ISE neo

	Predicate **ISE indirect Cl for Gen.2 on cobas c 501 (K060373)**	**Candidate** **ISE indirect Cl for Gen.2 on cobas ISE neo (K253491)**
Proprietary name	ISE indirect Cl for Gen.2	Same
Intended use	The ISE analytical unit of the Roche/Hitachi **cobas c** systems is intended for the quantitative determination of chloride in serum, plasma or urine using ion-selective electrodes.	The ISE analytical unit of the **cobas c** systems is intended for the quantitative determination of chloride in serum, plasma or urine using ion-selective electrodes.
Technology	ISE Potentiometry	Same
Test type	Quantitative	Same
Typical sample volumes	9.7 µL	15 µL
Default ISE Dilution ratio	1:31	Same
Sample handling system	Input of samples via core input buffer using universal sample racks	Same
Sample Identification	Barcode	Same
Measuring Range	Serum/Plasma: 60-140 mmol/L Urine: 20-250 mmol/L	Same

4. NON-CLINICAL PERFORMANCE EVALUATION

The non-clinical performance studies for ISE indirect Na for Gen.2, ISE indirect K for Gen.2, and ISE indirect Cl for Gen.2 are summarized below.

4.1. Precision

4.1.1. Repeatability and Intermediate Precision

Precision experiments were performed in accordance with CLSI guideline EP05-A3. Two aliquots per run, two runs per day for ≥ 21 days were performed on the **cobas** ISE neo analytical unit. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated.

Table 5: Summary of ISE Na Precision Results – Serum

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	116	0.714	0.6
PCCC2	139	0.830	0.6
Sample 1	87.0	0.404	0.5
Sample 2	132	0.817	0.6
Sample 3	136	0.793	0.6
Sample 4	159	0.797	0.5
Sample 5	176	0.811	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	116	1.40	1.2
PCCC2	140	1.41	1.0
Sample 1	86.5	1.49	1.7
Sample 2	132	1.07	0.8
Sample 3	137	0.984	0.7
Sample 4	159	1.24	0.8
Sample 5	175	1.30	0.7

Table 6: Summary of ISE Na Precision Results – Plasma

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	115	0.529	0.5
PCCC2	140	0.616	0.4
Sample 1	88.1	0.394	0.4
Sample 2	131	0.815	0.6
Sample 3	136	0.734	0.5
Sample 4	156	0.742	0.5
Sample 5	173	0.818	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	115	1.40	1.2
PCCC2	140	1.54	1.1
Sample 1	87.8	1.52	1.7
Sample 2	131	1.36	1.0
Sample 3	136	1.21	0.9
Sample 4	157	1.38	0.9
Sample 5	173	1.57	0.9

Table 7: Summary of ISE Na Precision Results – Urine

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	81.1	0.380	0.5
LiQ_UR2	171	0.947	0.6
Sample 1	27.0	0.295	1.1
Sample 2	135	0.492	0.4
Sample 3	111	0.432	0.4
Sample 4	198	0.847	0.4
Sample 5	237	1.02	0.4
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	81.1	1.17	1.4
LiQ_UR2	171	1.72	1.0
Sample 1	26.1	1.20	4.6
Sample 2	135	1.33	1.0
Sample 3	111	1.02	0.9
Sample 4	198	2.04	1.0
Sample 5	237	2.84	1.2

Table 8: Summary of ISE K Precision Results – Serum

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	3.65	0.0240	0.7
PCCC2	7.44	0.0405	0.5
Sample 1	1.76	0.0105	0.6
Sample 2	5.08	0.0279	0.6
Sample 3	3.64	0.0187	0.5
Sample 4	5.65	0.0286	0.5
Sample 5	9.70	0.0505	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	3.65	0.0606	1.7
PCCC2	7.48	0.0942	1.3
Sample 1	1.76	0.0556	3.2
Sample 2	5.12	0.0674	1.3
Sample 3	3.64	0.0432	1.2
Sample 4	5.65	0.0583	1.0
Sample 5	9.76	0.0815	0.8

Table 9: Summary of ISE K Precision Results – Plasma

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	3.62	0.0194	0.5
PCCC2	7.44	0.0327	0.4
Sample 1	1.69	0.0126	0.7
Sample 2	5.03	0.0342	0.7
Sample 3	3.50	0.0221	0.6
Sample 4	5.56	0.0253	0.5
Sample 5	9.70	0.0527	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	3.65	0.0556	1.5
PCCC2	7.49	0.0947	1.3
Sample 1	1.69	0.0592	3.5
Sample 2	5.06	0.0561	1.1
Sample 3	3.52	0.0485	1.4
Sample 4	5.56	0.0579	1.0
Sample 5	9.77	0.0866	0.9

Table 10: Summary of ISE K Precision Results – Urine

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	30.3	0.208	0.7
LiQ_UR2	71.7	0.673	0.9
Sample 1	3.51	0.0527	1.5
Sample 2	48.5	0.394	0.8
Sample 3	29.3	0.239	0.8
Sample 4	75.2	0.609	0.8
Sample 5	88.3	0.772	0.9
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	30.3	0.597	2.0
LiQ_UR2	71.7	2.00	2.8
Sample 1	3.51	0.0611	1.7
Sample 2	48.5	1.22	2.5
Sample 3	29.3	0.510	1.7
Sample 4	75.2	2.09	2.8
Sample 5	88.3	2.67	3.0

Table 11: Summary of ISE Cl Precision Results – Serum

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	85.9	0.560	0.7
PCCC2	107	0.652	0.6
Sample 1	68.0	0.322	0.5
Sample 2	104	0.463	0.4
Sample 3	97.8	0.461	0.5
Sample 4	114	0.613	0.5
Sample 5	138	0.651	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	85.9	1.21	1.4
PCCC2	107	1.27	1.2
Sample 1	68.0	1.07	1.6
Sample 2	104	0.938	0.9
Sample 3	97.8	0.935	1.0
Sample 4	114	1.05	0.9
Sample 5	138	1.11	0.8

Table 12: Summary of ISE Cl Precision Results – Plasma

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	86.2	0.454	0.5
PCCC2	107	0.455	0.4
Sample 1	65.0	0.301	0.5
Sample 2	101	0.632	0.6
Sample 3	94.5	0.541	0.6
Sample 4	110	0.497	0.5
Sample 5	135	0.735	0.5
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PCCC1	85.9	1.20	1.4
PCCC2	107	1.34	1.3
Sample 1	65.2	1.20	1.8
Sample 2	101	1.07	1.1
Sample 3	94.4	1.02	1.1
Sample 4	110	1.14	1.0
Sample 5	135	1.28	0.9

Table 13: Summary of ISE Cl Precision Results – Urine

Repeatability			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	82.3	0.402	0.5
LiQ_UR2	193	1.14	0.6
Sample 1	23.5	0.535	2.3
Sample 2	132	0.571	0.4
Sample 3	105	0.656	0.6
Sample 4	201	0.925	0.5
Sample 5	247	1.02	0.4
Intermediate Precision			
Sample	**Mean (mmol/L)**	**SD (mmol/L)**	**CV (%)**
LiQ_UR1	82.0	0.985	1.2
LiQ_UR2	193	2.12	1.1
Sample 1	23.5	1.63	7.0
Sample 2	132	1.33	1.0
Sample 3	106	1.10	1.0
Sample 4	202	2.01	1.0
Sample 5	247	3.51	1.4

4.2. Analytical Sensitivity

The Limit of Blank (LoB) of the ISE indirect Na-K-Cl for Gen.2 on the **cobas** ISE neo analytical unit were determined according to CLSI EP17-A2. The LoB is the highest observed measurement value for an analyte-free sample. The Limit of Blank was determined as the 95th percentile of measurements of blank samples.

The Limit of Detection (LoD) of the ISE indirect Na-K-Cl for Gen.2 on the **cobas** ISE neo analytical unit were determined according to CLSI EP17-A2. The LoD determines the lower limit for samples with analyte. The LoD was determined as the lowest amount of analyte in a sample that can be detected with a 95% probability.

The Limit of Quantitation (LoQ) of the the ISE indirect Na-K-Cl for Gen.2 on the **cobas** ISE neo analytical unit were determined according to CLSI EP17-A2. LoQ determines the lowest amount of analyte that can be quantitatively determined with stated accuracy and stated experimental

conditions. The LoQ was determined as the lowest concentration of analyte which can be quantified with a total error of no more than 30%.

Table 14: Summary of Results ISE Na, ISE K, ISE Cl, Sensitivity Limits

Sodium	
Limit of Blank	5.70 mmol/L
Limit of Detection	6.17 mmol/L
Limit of Quantitation	14.5 mmol/L
Potassium	
Limit of Blank	0.195 mmol/L
Limit of Detection	0.224 mmol/L
Limit of Quantitation	0.891 mmol/L
Chloride	
Limit of Blank	2.70 mmol/L
Limit of Detection	3.42 mmol/L
Limit of Quantitation	10.3 mmol/L

4.3. Linearity/Assay Reportable Range

Linearity studies were conducted to demonstrate that measurements across the claimed measuring range for each parameter are linear. The studies were performed according to CLSI guideline EP06-Ed2. Linearity was confirmed for the following measuring ranges:

Serum/Plasma:

Na 80 – 180 mmol/L

K 1.5 – 10.0 mmol/L

Cl 60 – 140 mmol/L

Urine:

Na 20 – 250 mmol/L

K 3 – 100 mmol/L

Cl 20 – 250 mmol/L

4.4. Dilution

Post Dilution Check experiments were conducted to verify the automatic rerun function of the **cobas** ISE neo analytical unit. Post Dilution studies confirmed to following extended measuring intervals:

Na 251 – 375 mmol/L

K 101 – 150 mmol/L

Cl 251 – 375 mmol/L

4.5. Endogenous Interferences

The effects of interference by endogenous substances bilirubin, ditaurobilirubin, hemolysis and lipemia on the ISE indirect Na-K-Cl for Gen.2 were determined on the **cobas** ISE neo analytical unit using pooled human plasma and serum and urine (where applicable) samples spiked with varying levels of interferent.

Table 15: Summary of Endogenous Interferences – ISE Na

Serum		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	119
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	159
Hemolysis [Level 1]	1771 [H-Index]	106
Hemolysis [Level 2]	1771 [H-Index]	138
Lipemia [Level 1]	2279 [L-Index]	104
Lipemia [Level 2]	2279 [L-Index]	138
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	119
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	156
Plasma		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	120
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	159
Hemolysis [Level 1]	1771 [H-Index]	106
Hemolysis [Level 2]	1771 [H-Index]	137
Lipemia [Level 1]	2279 [L-Index]	103
Lipemia [Level 2]	2279 [L-Index]	139
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	118
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	156
Urine		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Hemolysis [Level 1]	1227 [H-Index]	64.9
Hemolysis [Level 2]	1227 [H-Index]	183

Table 16: Summary of Endogenous Interferences – ISE K

Serum		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	3.52
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	6.96
Hemolysis [Level 1]	23.0 [H-Index]	3.73
Hemolysis [Level 2]	23.0 [H-Index]	6.26
Lipemia [Level 1]	2279 [L-Index]	3.07
Lipemia [Level 2]	2279 [L-Index]	5.83
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	3.42
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	6.43
Plasma		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	2.96
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	7.31
Hemolysis [Level 1]	23.0 [H-Index]	3.72
Hemolysis [Level 2]	23.0 [H-Index]	6.27
Lipemia [Level 1]	2279 [L-Index]	2.55
Lipemia [Level 2]	2279 [L-Index]	5.74
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	2.89
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	6.32
Urine		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Hemolysis [Level 1]	23.0 [H-Index]	23.4
Hemolysis [Level 2]	23.0 [H-Index]	85.0

Table 17: Summary of Endogenous Interferences – ISE Cl

Serum		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	85.4
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	119
Hemolysis [Level 1]	1771 [H-Index]	74.0
Hemolysis [Level 2]	1771 [H-Index]	103
Lipemia [Level 1]	2279 [L-Index]	74.2
Lipemia [Level 2]	2279 [L-Index]	103
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	82.6
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	114
Plasma		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Conjugated Bilirubin [Level 1]	70.0 [I-Index]	88.5
Conjugated Bilirubin [Level 2]	70.0 [I-Index]	123
Hemolysis [Level 1]	1771 [H-Index]	74.6
Hemolysis [Level 2]	1771 [H-Index]	104
Lipemia [Level 1]	2279 [L-Index]	76.3
Lipemia [Level 2]	2279 [L-Index]	108
Unconjugated Bilirubin [Level 1]	77.0 [I-Index]	85.5
Unconjugated Bilirubin [Level 2]	77.0 [I-Index]	120
Urine		
Potential Interferent	**No Interference up to**	**Observed Sample Conc (mmol/L)**
Hemolysis [Level 1]	1227 [H-Index]	66.6
Hemolysis [Level 2]	1227 [H-Index]	191

4.6. Exogenous Interferences – Drugs

Drug Interference studies were conducted to evaluate drugs for potential interference with ISE indirect Na-K-Cl for Gen.2 measured on the **cobas** ISE neo analytical unit. The following interference claims were verified:

Table 18: Drug Interferences – Serum Panel

Drug	Concentration tested
Acetaminophen	200 mg/L
Acetylsalicylic acid	1000 mg/L
Ampicillin-Na	1000 mg/L
Ascorbic acid	300 mg/L
Cefoxitin	2500 mg/L
Cyclosporine	5 mg/L
Doxycyclin	50 mg/L
Heparin	5000 IU/L
Ibuprofen	500 mg/L
Intralipid	10000 mg/L
Levodopa	20 mg/L
Methyldopa	20 mg/L
Metronidazole	200 mg/L
N-Acetylcysteine	1600 mg/L
Phenylbutazone	400 mg/L
Rifampicin	60 mg/L
Theophylline	100 mg/L

Table 19: Drug Interferences – Urine Panel

Drug	Concentration tested
Acetaminophen	3000 mg/L
Ascorbic acid	4000 mg/L
Cefoxitin	12000 mg/L
Gentamycine sulfate	400 mg/L
Ibuprofen	4000 mg/L
Levodopa	1000 mg/L
Methyldopa	2000 mg/L
N-Acetylcysteine	10 mg/L
Ofloxacine	900 mg/L
Phenazopyridine	300 mg/L
Salicyluric acid	6000 mg/L
Tetracycline	300 mg/L

4.7. Sample Matrix Comparison

The effect of the presence of anticoagulants on analyte recovery were determined by method comparison on the **cobas** ISE neo analytical unit, obtained from samples drawn into Li-Heparin Plasma and Serum collection tubes. The following results were obtained.

Table 20: Summary of Matrix Comparison Passing/Bablok Results

Sodium			
Comparison	**Slope**	**Intercept**	**Coefficient r**
Serum vs. Serum w/Gel Separation Tube	1.009	-1.41	0.995
Serum vs. Li-Heparin Plasma	1.00	-0.300	0.998
Potassium			
Comparison	**Slope**	**Intercept**	**Coefficient r**
Serum vs. Serum w/Gel Separation Tube	0.996	0.0161	0.997
Flame Photometry vs. Li-Heparin Plasma	1.000	-0.070	0.997
Chloride			
Comparison	**Slope**	**Intercept**	**Coefficient r**
Serum vs. Serum w/Gel Separation Tube	1.000	-0.0500	0.991
Serum vs. Li-Heparin plasma	0.997	-0.0137	0.995

4.8. Method Comparison to Predicate

Method Comparison experiments were performed for all sample types using ISE Na on the ISE neo versus ISE indirect Na for Gen2. on **cobas pro** ISE and flame photometry to assess the bias.

Method Comparison experiments were performed for all sample types using ISE K on the ISE neo versus ISE indirect K for Gen2. on **cobas c** 501 and flame photometry to assess the bias.

Method Comparison experiments were performed for all sample types using ISE Cl on the ISE neo versus ISE indirect Cl for Gen2. on **cobas c** 501 and coulometry to assess the bias. The results can be found below:

Table 21: Summary of Method Comparison – Sodium

Sodium					
Instruments	**Sample Type/N**	**Min x**	**Max x**	**P/B Regression**	**Coeff. (r)**
(x) Flame photom. (y) **cobas** ISE neo	Plasma / 118	79.5	177	y = 0.967x + 5.07	0.987
Bias at 135 mmol/L = 0.591 (0.4 %) Bias at 155 mmol/L = -0.073 (0.0 %)					
(x) **cobas pro** ISE (y) **cobas** ISE neo	Plasma / 119	80.5	176	y = 1.000x + 0.500	0.999
Bias at 135 mmol/L = 0.500 (0.4 %) Bias at 155 mmol/L = 0.500 (0.3 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Plasma / 118	85.0	176	y = 0.987x + 1.60	0.999
Bias at 135 mmol/L = -0.123 (-0.1 %) Bias at 155 mmol/L = -0.377 (-0.2 %)					
(x) Flame photom. (y) **cobas** ISE neo	Serum / 117	85.4	182	y = 0.950x + 5.83	0.989
Bias at 135 mmol/L = -0.888 (-0.7 %) Bias at 155 mmol/L = -1.88 (-1.2 %)					
(x) **cobas pro** ISE (y) **cobas** ISE neo	Serum / 119	80.7	178	y = 1.002x + 0.393	0.999
Bias at 135 mmol/L = 0.699 (0.5 %) Bias at 155 mmol/L = 0.744 (0.5 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Serum / 120	80.8	178	y = 1.009x - 1.31	0.999
Bias at 135 mmol/L = -0.112 (-0.1 %) Bias at 155 mmol/L = 0.0658 (0.0 %)					
(x) Flame photom. (y) **cobas** ISE neo	Urine / 100	25.4	238	y = 1.009x + 0.529	0.999
(x) **cobas pro** ISE (y) **cobas** ISE neo	Urine / 118	20.9	239	y = 1.010x - 0.555	1.000
(x) **cobas c** 501 (y) **cobas** ISE neo	Urine / 116	24.1	238	y = 1.003x + 0.262	1.000

Table 22: Summary of Method Comparison – Potassium

Potassium					
Instruments	**Sample Type/N**	**Min x**	**Max x**	**P/B Regression**	**Coeff. (r)**
(x) Flame photom. (y) **cobas** ISE neo	Plasma / 106	1.59	10.1	y = 1.027x - 0.0254	0.998
Bias at 3.5 mmol/L = 0.0689 (2.0 %) Bias at 5.5 mmol/L = 0.123 (2.2 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Plasma / 116	1.64	9.69	y = 1.000x - 0.0400	0.999
Bias at 3.5 mmol/L = -0.0400 (-1.1 %) Bias at 5.5 mmol/L = -0.0400 (-0.7 %)					
(x) Flame photom. (y) **cobas** ISE neo	Serum / 101	1.56	9.69	y = 1.009x + 0.0155	0.998
Bias at 3.5 mmol/L = 0.0465 (1.3 %) Bias at 5.5 mmol/L = 0.0642 (1.2 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Serum / 118	1.62	9.93	y = 1.000x - 0.0400	1.000
Bias at 3.5 mmol/L = -0.0400 (-1.1 %) Bias at 5.5 mmol/L = -0.0400 (-0.7 %)					
(x) Flame photom. (y) **cobas** ISE neo	Urine / 106	3.20	95.6	y = 1.042x - 0.0282	0.999
(x) **cobas c** 501 (y) **cobas** ISE neo	Urine / 113	3.41	93.4	y = 1.056x - 0.777	1.000

Table 23: Summary of Method Comparison – Chloride

Chloride					
Instruments	**Sample Type/N**	**Min x**	**Max x**	**P/B Regression**	**Coeff. (r)**
(x) Coulometer (y) **cobas** ISE neo	Plasma / 117	66.0	138	y = 0.992x + 1.16	0.988
Bias at 95 mmol/L = 0.397 (0.4 %) Bias at 110 mmol/L = 0.276 (0.3 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Plasma / 119	62.4	137	y = 1.010x + 0.152	0.999
Bias at 95 mmol/L = 1.14 (1.2 %) Bias at 110 mmol/L = 1.29 (1.2 %)					
(x) Coulometer (y) **cobas** ISE neo	Serum / 108	63.0	132	y = 0.950x + 5.82	0.986
Bias at 95 mmol/L = 1.08 (1.1 %) Bias at 110 mmol/L = 0.325 (0.3 %)					
(x) **cobas c** 501 (y) **cobas** ISE neo	Serum / 115	63.1	139	y = 1.021x - 1.41	0.998
Bias at 95 mmol/L = 0.593 (0.6 %) Bias at 110 mmol/L = 0.908 (0.8 %)					
(x) Coulometer (y) **cobas** ISE neo	Urine / 117	21.0	240	y = 1.033x – 3.12	0.999
(x) **cobas c** 501 (y) **cobas** ISE neo	Urine / 118	22.6	248	y = 1.004x - 1.20	1.000

4.9. Stability

The stability studies and acceptance criteria have been reviewed and found to be acceptable. The stability data supports Roche Diagnostic's claims as reported in the package labeling.

5. ADDITIONAL INFORMATION

The ISE indirect Na-K-Cl for Gen.2 is intended to be used with the following:

- ISE Reference Electrolyte
- ISE Internal Standard Gen.2 conc.
- ISE Cleaning Solution
- Deproteinizer
- Activator
- ISE Standard Low
- ISE Standard High
- PreciControl ClinChem Multi 1
- PreciControl ClinChem Multi 2

6. CONCLUSIONS

The analytical performance data for ISE indirect Na-K-Cl for Gen.2 on **cobas** pro integrated solutions support a substantial equivalence decision.