August 16, 2019

Roche Diagnostics
Khoa Tran
Regulatory Affairs Principal
9115 Hague Road
Indianapolis, IN 46250

Re: K191899
Trade/Device Name: Glucose HK Gen.3
ISE indirect Na for Gen.2
Elecsys TSH,
cobas pro integrated solutions
Regulation Number: 21 CFR 862.1345
Regulation Name: Glucose test system
Regulatory Class: Class II
Product Code: CFR, JGS, JLW, JJE
Dated: July 15, 2019
Received: July 16, 2019

Dear Khoa Tran:

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 (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 located 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.

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 803) for devices or postmarketing safety reporting (21 CFR 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 systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 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,

Kellie B. Kelm, Ph.D.
Acting Director
Division of Chemistry and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k191899

Device Name
cobas pro integrated solutions
Glucose HK Gen.3; ISE indirect Na for Gen.2
Elecsys TSH

Indications for Use *(Describe)*
The cobas pro integrated solutions is an IVD device used for the quantitation of clinical chemistry/ immunochemistry and Ion Selective Electrolyte parameters from various biological fluids.

Glucose HK Gen.3 is an in vitro test for the quantitative determination of glucose in human serum, plasma, urine and CSF on Roche/Hitachi cobas c systems. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, idiopathic hypoglycemia and pancreatic islet cell tumors.

The ISE indirect Na for Gen. 2 is intended for the quantitative determination of sodium 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.

Elecsys TSH immunoassay is intended for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders. The electrochemiluminescence immunoassay “ECLIA” is intended for use on cobas e immunoassay analyzers.

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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cobas pro integrated solutions
k191899 510(k) Summary

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

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the previously cleared Glucose, Sodium, and TSH assays on the **cobas pro** integrated solutions.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250
Contact	Khoa Tran Phone: (317) 521-3409 Fax : (317) 521-2324 Email : khoa.tran@roche.com Secondary Contact: Dave Tribbett Phone: (317) 521-2964 Fax : (317) 521-2324 Email: david.tribbett@roche.com
Date Prepared	August 16, 2019
Proprietary Name	**cobas pro** integrated solutions Glucose HK Gen.3 ISE indirect Na for Gen.2 Elecsys TSH
Common Name	**cobas pro** integrated solutions, ISE Na, GLUC3, TSH
Classification Name	• Hexokinase, glucose • Electrode, ion specific, sodium • Radioimmunoassay, thyroid-stimulating hormone • Analyzer, chemistry (photometric, discrete), for clinical use
Regulation Numbers, Regulation Name, Regulatory Class and Product Codes	• 21 CFR 862.1345, Glucose test system, Class II, CFR, • 21 CFR 862.1665, Sodium test system, Class II, JGS • 21 CFR 862.1690, Thyroid stimulating hormone test system, Class II, JLW • 21 CFR 862.2160, Discrete photometric chemistry analyzer for clinical use, Class I, JJE
Predicate Device(s)	**cobas** 6000 analyzer series Glucose HK ISE Indirect Elecsys TSH
Establishment Registration	For the **cobas pro** integrated solutions, Glucose HK, ISE indirect Na and Elecsys TSH, the establishment registration number for Roche Diagnostics GmbH in Mannheim, Germany is 9610126, and for Penzberg, Germany, 9610529. The establishment registration number for Roche Diagnostics in the United States is 1823260.

Device Description

1.1. System

The **cobas pro** integrated solutions (**cobas pro**) is a fully automated, random-access, software controlled system intended for in vitro quantitative analysis of analytes in body fluids. It will typically be used in clinical laboratories with large workload. The system consolidates clinical chemistry, homogenous and heterogeneous immunoassays as well as electrolyte testing within one workplace. It consists of a high throughput sample distribution unit (core unit) and different analytical units for ISE (cobas pro ISE analytical unit), clinical chemistry (c 503 analytical unit) and immunoassay (e 801 analytical) testing. The system hardware is comprised of new or previously cleared members of the Roche/Hitachi cobas c or Elecsys families of analyzers. The instrument software is unique to the **cobas pro** and was developed from previous generations of Roche/Hitachi instrument systems.

Instrument Description Information

a. Instrument Name:

   cobas pro integrated solutions

b. Specimen Identification:

   The specimen is in a tube with a barcode label. The system identifies specimen by scanning the barcode.

c. Specimen Sampling and Handling:

   The specimen is in a tube with the barcode label facing the side with the open slot of the rack. The rack is assigned with ID number and barcode.

d. Calibration:

   The software of the cobas pro integrated solution automatically recommends calibration for all tests requiring calibration. Calibration may also be ordered manually at any time. The software recommends calibrations according to the application parameters for the

assay. The system checks the validity of each calibration automatically. If the calibration was successful, the calibrated tests are valid and the system continues operation. Calibration is specific to each analytical unit, measuring channel, and reagent.

The calibrators are loaded onto a 5-position calibrator rack and loaded onto the system. The system automatically recognizes the specially designated (black) calibration rack. The calibrator solutions are specific to the assay and identified in the method sheet of each assay. Multi-calibrator solutions are available to calibrate multiple applications. The available calibration modes are linear and non-linear full calibration, 1- and 2-point recalibration, and automatic full calibration. The calibration type differs depending on the reagent assay and is coded into the application parameter file for each reagent application and is described in the method sheet for each reagent assay application. The recommended calibration frequency is described in the method sheet for each reagent assay application.

e. Quality Controls:

The system can be set up to recommend QC measurements based on test-specific timeout intervals. The method sheet for each assay used on the system contains QC recommendations for the specific application. The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits. Follow the applicable government regulations and local guidelines for quality control.

1.2. Reagent

Glucose HK Gen.3

Glucose is phosphorylated by hexokinase (HK) in the presence of adenosine triphosphate (ATP) and magnesium ions to produce glucose-6-phosphate (G-6-P) and adenosine diphosphate (ADP). Glucose-6-phosphate dehydrogenase (G-6-PDH) specifically oxidizes G-6-P to 6-phosphogluconate with the concurrent reduction of nicotinamide adenine dinucleotide

(NAD) to nicotinamide adenine dinucleotide reduced (NADH). One micromole of NADH is produced for each micromole of glucose consumed. The NADH produced absorbs light at 340 nm and can be detected spectrophotometrically as an increased absorbance.

The reagent working solutions include:

- R1 MES buffer: 5.0 mmol/L, pH 6.0; Mg2+, 24 mmol/L; ATP, ≥ 4.5 mmol/L; NADP, ≥ 7.0 mmol/L; preservative
- R3 HEPES buffer: 200 mmol/L, pH 8.0; Mg2+, 4 mmol/L; HK (yeast), ≥ 300 µkat/L; G‑6‑PDH (E. coli), ≥ 300 µkat/L; preservative

ISE indirect Na for Gen.2

The ISE module for Na^+ employs 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.

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. 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.

ISE Auxiliary Reagents include:

- ISE Reference Electrolyte: 1 mol/L potassium chloride
- ISE Diluent: HEPES buffer, 10 mmol/L; Triethanolamine, 7 mmol/L; Preservative
- ISE Internal Standard: HEPES buffer, 10 mmol/L; Triethanolamine, 7 mmol/L; Sodium chloride, 3.06 mmol/L; Sodium acetate, 1.45 mmol/L; Potassium chloride, 0.16 mmol/L; Preservative

- ISE Cleaning Solution: Sodium hydroxide solution, 3 mol/L with sodium hypochlorite solution < 2 % active Cl
- ISE Deproteinizer: Sodium hydroxide solution, approximately 1.2 % active Cl
- Electrodes: Sodium, Reference

Elecsys TSH

The Elecsys TSH immunoassay makes use of a sandwich test principle using monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex) consist of a chimeric construct from human and mouse specific components. The Elecsys TSH immunoassay is used for the in vitro quantitative determination of thyroid stimulating hormone in human serum and plasma. It is intended for use on the **cobas e** immunoassay analyzers.

The reagent working solutions include:

Rack Pack (kit placed on the analyzer)

- M: Streptavidin-coated microparticles, 1 bottle, 14.1 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1: Anti-TSH-Ab~biotin, 1 bottle, 15.8 mL: Biotinylated monoclonal anti TSH antibody (mouse) 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.
- R2: Anti-TSH-Ab~Ru(bpy), 1 bottle, 13.9 mL: Monoclonal anti TSH antibody (mouse/human) labeled with ruthenium complex 1.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

2. INDICATIONS FOR USE

2.1. Reagents

Glucose HK Gen.3

In vitro test for the quantitative determination of glucose in human serum, plasma, urine and CSF on Roche/Hitachi **cobas c** systems.

Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, idiopathic hypoglycemia and pancreatic islet cell tumors.

ISE indirect Na for Gen.2

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.

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.

Elecsys TSH

Elecsys TSH immunoassay is intended for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

2.2. System

The **cobas pro** integrated solutions is an IVD device used for the quantitation of clinical chemistry/ immunochemistry and Ion Selective Electrolyte parameters from various biological fluids.

3. TECHNOLOGICAL CHARACTERISTICS

The following table lists the technical characteristics from the assays method sheets.

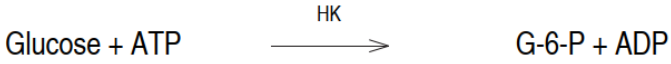
Table 1: Assays Technical Characteristics

Feature	Assays
	ISE indirect Na
Technology	Potentiometry
Application/test time	12 sec
Instrument platform	**cobas pro** ISE
Test type	Quantitative
Assay protocol	Sample + ISE Diluent
Handling of R1 and R2	Liquid, ready to use
Sample type/matrix	Serum, plasma, and urine
Measuring Range	80-180 mmol/L (Serum/Plasma); 20-250 mmoL (Urine)
	Glucose HK Gen.3 (GLUC3)
Technology	Photometric
Application/test time	10 minutes
Instrument platform	**cobas c** 503 analytical unit
Test type	Quantitative
Assay protocol	R1+R3+sample+Diluent
Handling of R1 and R3	Liquid, ready to use
Sample type/matrix	Serum, plasma, urine and CSF
Measuring Range	2-750 mg/dL (0.11-41.6 mmol/L)
	Elecsys TSH
Technology	ECLIA
Application/test time	18 minutes
Instrument platform	**cobas e** immunoassay analyzers
Test format	Sandwich
Test type	Quantitative
Assay protocol	R1+R2+sample, incubation, +beads, incubation
Handling of R1 and R2	Liquid, ready to use
Sample type/matrix	Serum and plasma
Measuring Range	0.005-100 µIU/mL

Assay Principle of Operation

Glucose

The Glucose Hexokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate by ATP.



Glucose-6-phosphate dehydrogenase oxidizes glucose-6-phosphate in the presence of NADP to gluconate-6-phosphate dehydrogenase. No other carbohydrate is oxidized. The rate of NADPH formation during the reaction is directly proportional to the glucose concentration and is measure photometrically.

Sodium

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. The EMF develops and ion concentration is determined according to the Nernst equation.

TSH

The TSH assay is based on the sandwich principle of competition. The total duration of the assay is 18 minutes.

- 1st incubation: 50 µL of sample, a biotinylated monoclonal TSH- specific antibody and a monoclonal TSH- specific antibody labeled with a ruthenium complex react to form a sandwich complex.

- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument specifically generated by 2‑ point calibration and a master curve provided via the reagent barcode or e‑ barcode.

Table 2: Substantial Equivalency System

Topic	**cobas 6000 Analyzer Series (k060373)**	**cobas pro integrated solutions (k191899)**
Intended Use	Same	IVD device used for the quantitation of clinical chemistry/ immunochemistry and Ion Selective Electrolyte parameters from various biological fluids
Software	**cobas** 6000 Analyzer Series System Software	**cobas pro** integrated solutions system Software
Configuration	Several analytical units with one PC and one Core unit	Same as **cobas** 6000
Function performed	Data Input, Sample Processing, Result Calculation, Result Reporting, Quality Control, Infrastructure (power, water supply)	Same
PC (Controller Unit) Functions	Data Input (Keyboard, Disc), Data Output (Screen, printer)	Data Input (Touch screen, Disc), Data Output (Screen, printer)
Core Unit Functions	Real time database, data input and output (via HOST communication), control of sample conveyer	Same
Analytical Unit(s) Functions	Control of analytic processes (pipetting, incubation, detection) Primary Signal processing	Same
Data Storage	Real time database in Core Unit (storage of System and Application parameters, Calibration Data, QC Data, Sample Results, Alarm history)	Same

Topic	cobas 6000 Analyzer Series (k060373)	cobas pro integrated solutions (k191899)
Result Calculation	Automated measuring of signal using various methods according to automated calculation of concentration via calibration curve	Same
Flagging of errors	Available	Same
Units Controlled	**cobas c** 501 (with integrated ISE) and **cobas e** 601-analyzers	**cobas c** 503, **cobas e** 801, and **cobas pro ISE** analyzers
Initial cassette volume check (ICVC) for reagent pipetting	Available	Same
Data concept (Application parameter, calibrator, control value transfer)	Electronic transfer possible (user must accept transfer before parameter applied)	Same

Table 3: Substantial Equivalency Glucose HK Gen. 3

Item	Glucose HK Gen. 3 (c 501 in cobas 6000 core) k060373	Glucose HK Gen. 3 (c 503 in cobas pro core) k191899
Proprietary name	Glucose HK Gen. 3	Glucose HK Gen. 3
Catalog number	04404483190	08057800190
Intended use	In vitro test for the quantitative determination of glucose in human serum, plasma, urine and CSF on Roche/Hitachi cobas c systems.	In vitro test for the quantitative determination of glucose in human serum, plasma, urine and CSF on Roche/Hitachi cobas c systems.
Technology	Photometric	Same
Test format	Enzymatic	Same
Test type	Quantitative	Same
Assay protocol	R1+R2+Diluent+Sample, incubation	Same
Pipetting volume sample	15 µL	Same
Pipetting volume R1	28 µL	Same
Pipetting volume R2	10 µL	Same
	Serum, plasma, urine and CSF	Same

Item	Glucose HK Gen. 3 (c 501 in cobas 6000 core) k060373	Glucose HK Gen. 3 (c 503 in cobas pro core) k191899
Handling of R1 and R2	Liquid, ready to use	Same
Measuring Range	0.11-41.6 mmol/L	Same

Table 4: Substantial Equivalency ISE indirect Na for Gen.2

Item	cobas c 501 ISE (in cobas 6000 core) k060373	cobas pro ISE (in cobas pro core) k191899
Proprietary name	ISE indirect Na	ISE indirect Na
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 Roche/Hitachi 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
Typical sample volumes	9.7 µL 15 µL	9.7 µL 15 µL
Default ISE Dilution ratio 1:31	1:31 (9.7uL sample + 291uL Diluent)	Same (15 uL sample + 450uLDiluent)
Sample types	Serum, plasma, urine	Same
Sample handling system	Input of samples via core input buffer using universal sample racks	Same
Measuring Range	Serum/Plasma: 80-180 mmol/L Urine: 20-250 mmol/L	Same

Table 5: Substantial Equivalency Elecsys TSH

Item	Elecsys TSH (e 801 in cobas 8000 core) k190773	Elecsys TSH (e 801 in cobas pro core) k191899
Proprietary name	Elecsys TSH	Elecsys TSH
Catalog number	08429324160	08429324160

Item	Elecsys TSH (e 801 in cobas 8000 core) k190773	Elecsys TSH (e 801 in cobas pro core) k191899
Intended use	Elecsys TSH immunoassay is intended for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders. The Elecsys TSH immunoassay is an electrochemiluminescence immunoassay "ECLIA", which is intended for use on the **cobas e** immunoassay analyzers.	Immunoassay for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders. The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e** immunoassay analyzers.
Technology	ECLIA	Same
Test format	Sandwich	Same
Test type	Quantitative	Same
Assay protocol	R1+R2+sample, incubation, +beads, incubation	Same
Pipetting volume sample	50 µL	Same
Pipetting volume beads	40 µL	Same
Pipetting volume R1	60 µL	Same
Pipetting volume R2	50 µL	Same
Handling of R1 and R2	Liquid, ready to use	Same
Buffer composition R1	phosphate buffer 100 mmol/L	Same
Biotinylated antibody	MAK<TSH>M-TU1.20-F(ab')2-Bi(DDS*,mono)	MAK<TSH>M-TU1.20-F(ab')2-Bi(PEG24**,mono)
Buffer composition R2	phosphate buffer 100 mmol/L	No change
	Anti-Biotin Antibody; specific for free, unconjugated biotin ("scavenger antibody")	Same
Measuring Range	0.005-100 µIU/mL	Same
Biotin Tolerance	<25 ng/mL	1200 ng/mL

4. NON-CLINICAL PERFORMANCE EVALUATION

The non-clinical performance studies for the Glucose HK, ISE indirect Na and Elecsys TSH are summarized below.

4.1. Precision

Precision was performed based on guidance from the Clinical and Laboratory Standards Institute (CLSI) document EP05-A3. A summary of results for each assay is presented below.

Glucose HK Gen.3: Repeatability and Intermediate Precision

The precision of the Glucose HK Gen.3 was evaluated on one **cobas c** 503 analytical unit with one reagent lot. The protocol consisted of testing 2 replicates of each control (PreciControl ClinChem Multi 1 and PreciControl ClinChem Multi 2) and human serum per run, 2 runs per day for 21 days. The samples were run in randomized order on the analyzer. Human serum samples used were all native, single donors as well as pools. The protocol was repeated for urine and CSF applications. The Repeatability and Intermediate precision were calculated according to EP05-A3. All samples met the predetermined acceptance criterion. The data presented in the tables below is the worst precision result of the 3 lots.

Table 6: Glucose HK Gen.3 Summary of Repeatability and Intermediate Precision Results

Repeatability and Intermediate Precision					
Repeatability					
Serum Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
PreciControl ClinChem Multi 1 (PCCC1)	5.61	101	0.0315	0.568	0.6
PreciControl ClinChem Multi 2 (PCCC2)	12.6	227	0.0523	0.942	0.4
Serum 1	0.188	3.39	0.0174	0.313	9.2
Serum 2	3.57	64.3	0.0181	0.326	0.5
Serum 3	5.46	98.4	0.0233	0.420	0.4
Serum 4	19.6	353	0.121	2.18	0.6

Serum 5	38.6	696	0.188	3.39	0.5
Urine Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
LyQ_UR1	1.09	19.6	0.0215	0.387	2.0
LyQ_UR2	16.4	296	0.0655	1.18	0.4
Urine 1	0.227	4.09	0.0188	0.339	8.3
Urine 2	0.733	13.2	0.0143	0.258	1.9
Urine 3	4.10	73.9	0.0418	0.753	1.0
Urine 4	22.0	396	0.182	3.28	0.8
Urine 5	40.6	732	0.173	3.12	0.4
CSF Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
LiQ_CSF1	3.31	59.6	0.0119	0.214	0.4
LiQ_CSF2	1.66	29.9	0.00970	0.175	0.6
CSF 1	0.273	4.92	0.00831	0.150	3.0
CSF 2	2.16	38.9	0.0180	0.324	0.8
CSF 3	3.81	68.7	0.0172	0.310	0.5
CSF 4	20.2	364	0.0824	1.48	0.4
CSF 5	39.9	719	0.193	3.48	0.5
Intermediate					
Serum Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
PreciControl ClinChem Multi 1 (PCCC1)	5.61	101	0.0559	1.007	1.0
PreciControl ClinChem Multi 2 (PCCC2)	12.8	231	0.106	1.910	0.8
Serum 1	0.188	3.39	0.0188	0.339	10.0
Serum 2	3.57	64.3	0.0212	0.382	0.6
Serum 3	5.46	98.4	0.0297	0.535	0.5
Serum 4	19.6	353	0.136	2.45	0.7
Serum 5	38.6	696	0.216	3.89	0.6
Urine Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
LyQ_UR1	1.09	19.6	0.0278	0.501	2.5
LyQ_UR2	16.4	296	0.122	2.20	0.7
Urine 1	0.215	3.87	0.0183	0.330	8.5
Urine 2	0.744	13.4	0.0180	0.324	2.4
Urine 3	4.07	73.3	0.0478	0.861	1.2

Urine 4	22.0	396	0.452	8.15	2.1
Urine 5	40.4	728	0.344	6.20	0.8
CSF Application (N=84)	Mean Value		SD		CV %
Specimen	mmol/L	mg/dL	mmol/L	mg/dL	
LiQ_CSF1	3.34	60.2	0.0163	0.294	0.5
LiQ_CSF2	1.66	29.9	0.0109	0.196	0.7
CSF 1	0.273	4.92	0.00966	0.174	3.5
CSF 2	2.16	38.9	0.0212	0.382	1.0
CSF 3	3.81	68.7	0.0240	0.432	0.6
CSF 4	20.2	364	0.0994	1.79	0.5
CSF 5	39.9	719	0.230	4.14	0.6

ISE indirect Na: Repeatability and Intermediate Precision

Precision of the ISE indirect Na was evaluated on one **cobas pro** ISE analyzer with one reagent lot. The protocol consisted of testing 2 replicates of each control (PreciControl ClinChem Multi 1 and PreciControl ClinChem Multi 2) and Li-Heparin plasma, serum and urine per run, 2 runs per day for 21 days. The samples were run in randomized order on the analyzer. The plasma, serum and urine samples used were all native, single donors as well as pools. Repeatability and Intermediate precision were calculated according to EP05-A3. All samples met the predetermined acceptance criterion. The following table summarizes the precision data for the ISE indirect Na.

Precision of the ISE indirect Na for Gen.2 was evaluated on one cobas pro ISE with one reagent lot.

Table 7: ISE indirect Na Summary of Repeatability and Intermediate Precision Results

Repeatability and Intermediate Precision			
Repeatability			
Specimen (Li Hep Plasma) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PreciControl ClinChem Multi 1	112	0.285	0.3
PreciControl ClinChem Multi 2	136	0.484	0.4
Sample 1	86.3	0.479	0.6
Sample 2	131	0.348	0.3
Sample 3	137	0.298	0.2
Sample 4	151	0.392	0.3
Sample 5	177	0.497	0.3
Specimen (Serum) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PreciControl ClinChem Multi 1	111	0.280	0.3
PreciControl ClinChem Multi 2	134	0.412	0.3
Sample 1	82.5	0.449	0.5
Sample 2	131	0.413	0.3
Sample 3	136	0.388	0.3
Sample 4	151	0.472	0.3
Sample 5	175	0.638	0.4
Specimen (Urine) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
Liquichek 1	76.9	0.338	0.4
Liquichek 2	175	0.803	0.5
Sample 1	23.6	0.128	0.5
Sample 2	137	0.473	0.3
Sample 3	112	0.516	0.5
Sample 4	207	0.899	0.4
Sample 5	244	0.814	0.3

Intermediate Precision			
Specimen (Li Hep Plasma) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PreciControl ClinChem Multi 1	111	0.967	0.9
PreciControl ClinChem Multi 2	134	0.902	0.7
Sample 1	84.7	1.25	1.5
Sample 2	129	0.879	0.7
Sample 3	135	0.931	0.7
Sample 4	149	0.821	0.6
Sample 5	174	0.950	0.5
Specimen (Serum) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
PreciControl ClinChem Multi 1	111	1.16	1.0
PreciControl ClinChem Multi 2	134	1.07	0.8
Sample 1	83.0	1.38	1.7
Sample 2	131	0.930	0.7
Sample 3	135	1.02	0.8
Sample 4	150	0.802	0.5
Sample 5	173	0.948	0.5
Specimen (Urine) (N=84)	**Mean Concentration (mmol/L)**	**SD (mmol/L)**	**CV (%)**
Liquichek 1	78.1	1.06	1.4
Liquichek 2	175	1.05	0.6
Sample 1	24.8	1.19	4.8
Sample 2	136	0.941	0.7
Sample 3	111	0.941	0.8
Sample 4	204	1.23	0.6
Sample 5	241	1.63	0.7

Elecsys TSH: Repeatability and Intermediate Precision

Precision of the Elecsys TSH assay was evaluated on one **cobas e** 801 immunoassay analyzer with one reagent lot. The protocol consisted of testing 2 replicates of each control (PreciControl Universal and PC Thyro Sensitive) and human sera (HS) per run, 2 runs per day for 21 days. The samples were run in randomized order on the analyzer. Human serum samples used were all native, single donors as well as pools. Repeatability and Intermediate imprecision were calculated according to EP05-A3. All samples met the predetermined acceptance criterion. The following table summarizes the precision data for the Elecsys TSH.

Precision of the Elecsys TSH assay was evaluated on one **cobas e** 801 immunoassay analyzer with one reagent lot.

Table 8: Summary of Repeatability and Intermediate Precision Results

		Repeatability		Intermediate precision	
Sample (N=84)	Mean (µIU/mL)	SD (µIU/mL)	CV (%)	SD (µIU/mL)	CV (%)
Human serum 1	0.0133	0.000829	6.3	0.00155	11.7
Human serum 2	0.262	0.00447	1.7	0.00722	2.8
Human serum 3	3.95	0.0661	1.7	0.123	3.1
Human serum 4	57.3	1.50	2.6	2.24	3.9
Human serum 5	93.1	2.64	2.8	4.29	4.6
PC Universal 1	1.32	0.023	1.7	0.0319	2.4
PC Universal 2	8.00	0.142	1.8	0.234	2.9
PC Thyro Sensitive	0.168	0.00274	1.6	0.00488	2.9

4.2. Analytical Sensitivity

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17 A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte‑free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte‑free samples are found with a probability of 95 %. The Limit of Blank was determined on the respective analytical unit, six runs on ≥ three days, with five blank samples with two replicates each per run. In total, 60 determinations for analyte free samples have been obtained.

The Limit of Detection was determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95%). The Limit of Detection was determined on the respective analytical unit, five samples

with low-analyte concentration was measured in two-fold determination in 6 runs, distributed over 3 days. In total 60 measurements were obtained per sample type.

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 20% (Glucose and TSH) and 30% (Sodium).

Samples with low analyte concentration are measured over 3 to 5 days on the respective analyzer ($n \geq 60$ per sample type). The mean value, SD, and %TE (total error) were calculated for each sample. The mean concentration is plotted versus the %TE, with LoQ determined at maximum allowable %TE.

A summary of empirical results for **Glucose HK Gen. 3** is presented below in the following order: LoB, LoD and LoQ.

Serum	**Reagent Lot**	**LoB [mg/dL]**
	Lot 3	0.2
	Lot 1	0.1
	Lot 2	0.2
Urine	**Reagent Lot**	**LoB [mg/dL]**
	Lot03	0.7
	Lot01	0.3
	Lot02	0.3
CSF	**Reagent Lot**	**LoB [mg/dL]**
	Lot 3	0.2
	Lot 1	0.2
	Lot 2	0.2

Serum	**Reagent Lot**	**LoD [mg/dL]**
	Lot 3	0.4
	Lot 1	0.3
	Lot 2	0.4
Urine	**Reagent Lot**	**LoD [mg/dL]**
	Lot03	1.0
	Lot01	0.6
	Lot02	0.6
CSF	**Reagent Lot**	**LoD [mg/dL]**
	Lot 3	0.3
	Lot 1	0.3
	Lot 2	0.3

Serum/Plasma	**Reagent Lot**	**LoQ [mg/dL]**
	Lot 3	1.3
	Lot 1	1.3
	Lot 2	1.4
Urine	**Reagent Lot**	**LoQ [mg/dL]**
	Lot03	1.4
	Lot01	1.3
	Lot02	1.5
CSF	**Reagent Lot**	**LoQ [mg/dL]**
	Lot 3	1.1
	Lot 1	1.1
	Lot 2	1.2

The results and labeling Claim for **Glucose HK Gen.3**

	Result	**Claim**
Limit of Blank (LoB)	0.2 mg/dL (0.011 mmol/L)	2 mg/dL (0.11 mmol/L)
Limit of Dection (LoD)	0.4 mg/dL (0.022 mmol/L)	2 mg/dL (0.11 mmol/L)
Limit of Quantitatiion (LoQ)	1.4 mg/dL (0.078 mmol/L)	2 mg/dL (0.11 mmol/L)

A summary of empirical results for **ISE indirect Na for Gen.2** is presented below in the following order: LoB, LoD and LoQ.

Sample Type	Electrode Lot	LoB [mmol/L]
Plasma	E9012	3.50
Serum	E9012	3.50
Urine	E9012	3.50

Sample Type	Electrode Lot	LoD [mmol/L]
Plasma	E9012	4.44
Serum	E9012	4.42
Urine	E9012	4.51

Sample Type	Electrode Lot	LoQ [mmol/L]
Plasma	E9012	11.8
Serum	E9012	12.1
Urine	E9012	12.2

Labeling Claim for **ISE indirect Na for Gen.2** as stated in the method sheet:

- Limit of Blank = 3.5 mmol/L
- Limit of Detection = 4.5 mmol/L
- Limit of Quantitation = 12.2 mmol/L

A summary of empirical results for **Elecsys TSH** is presented below in the following order: LoB, LoD and LoQ.

Reagent Lot	LoB (µIU/mL)
344546	0.0013
344548	0.0015
344550	0.0014

Reagent Lot	LoD (µIU/mL)

344546	0.00282
344548	0.00348
344550	0.00312

Reagent Lot	LoQ (µIU/mL)
344546	0.00410
344548	0.00386
344550	0.00495

Labeling Claim for **Elecsys TSH** as stated in the method sheet:

- Limit of Blank = 0.0025 µIU/mL
- Limit of Detection = 0.005 µIU/mL
- Limit of Quantitation = 0.005 µIU/mL

4.3. Linearity/Assay Reportable Range

Glucose HK Gen.3 (GLUC3)

Linearity was determined based on guidance from Clinical and Laboratory Standards Institute (CLSI) document EP06-A. Three high analyte human serum, urine and CSF samples were diluted to 12 levels covering the measuring range and were then measured. The aliquots were assayed in 3-fold determination within a single run. All deviations were within predetermined acceptance criteria. Linearity for serum, urine and CSF samples was confirmed in the claimed measuring range from 2.0 to 750 mg/dL (0.11 to 41.6 mmol/L).

Glucose HK Gen.3 (GLUC3)

- Serum: The mean observed linear range concentrations ranged from 0.0 to 783.0 mg/dL for the sample set. The correlation with the expected concentrations according to the linear regression formulas: Serum: $y = 0.999(x) + 0.00856$; $R^2 = 0.9999$.

- Urine: The mean observed linear range concentrations ranged from 0.0 to 788.4 mg/dL for the sample set. The correlation with the expected concentrations according to the linear regression formulas: Urine: $y = 0.999(x) + 0.00435$; $R^2 = 0.9997$.

- CSF: The mean observed linear range concentrations ranged from 0.00 to 829.8 mg/dL for the sample set. The correlation with the expected concentrations according to the linear regression formulas: CSF: $y = 0.998(x) + 0.0126$; $R^2 = 0.9992$

ISE indirect Na for Gen.2

Linearity was determined based on guidance from Clinical and Laboratory Standards Institute (CLSI) document EP06-A. Three high analyte human serum, urine and CSF samples were diluted to multiple aliquot concentrations covering the measuring range and were then measured. The aliquots were assayed in 3-fold determination within a single run. All deviations were within predetermined acceptance criteria. Linearity for Lithium heparin plasma and serum, and urine samples was confirmed in the claimed measuring range from 80-180 mmol/L and 20-250 mmol/L respectively.

- *Plasma*: The mean observed linear range concentrations ranged from 75.2 to 185 mmol/L for the sample set. The correlation with the expected concentrations according to the linear regression formulas: Plasma: $y = 1.000(x) + 0.0$; $R^2 = 0.9998$.
- *Serum*: The mean observed linear range concentrations ranged from 75.7 to 186 mmol/L for the sample set. The correlation with the expected concentrations according to the linear regression formulas: Serum: $y = 1.000(x) + 0.0$; $R^2 = 0.9998$.
- *Urine*: The mean observed linear range concentrations ranged from 13.7 to -265 mmol/L for the sample set. The correlation with the expected concentrations according to the linear regression formulas: Urine: $y = 1.000(x) + 0.0$; $R^2 = 0.9999$.

Elecsys TSH

Linearity of the Elecsys TSH assay was assessed on the **cobas e** 801 analytical unit according to CLSI EP06-A. Three high analyte human serum samples were diluted and concentrations covering the measuring range were measured. Samples were assayed in 3-fold determination within a single run.

- Serum: The linear range for the three human serum samples is 0.004 – 118 µIU/mL. Elecsys TSH correlated with expected concentrations according to the linear regression formulas: Serum: y = 1.082(x) -0.000156; R^2 = 0.9972

4.4. High Dose Hook Effect

The high-dose hook effect of the Elecsys TSH assay was assessed on the **cobas e** 801 analytical unit in one-fold determination. Three human serum samples were spiked with analyte to achieve high TSH concentrations. For each sample, a dilution series was performed. No hook effect up to 1466 µIU/mL TSH.

4.5. Endogenous Interference

The purpose of this study was to evaluate endogenous substances for potential interference with the parameters measured with the Glucose HK on **cobas c** 503, ISE indirect Na on **cobas pro** ISE, and Elecsys TSH on the **cobas e** 801 analytical units. All the endogenous substances met the acceptance criteria of recovery of 100±10%.

Glucose HK

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Glucose HK Gen.3 (GLUC3) assay was determined on the **cobas pro c** 503 analytical unit using plasma and urine samples and conducted according to CLSI EP07-A2. Glucose levels of approximately 79.5 mg/dL and 116.3 mg/dL were tested and the summary of results is presented in the two tables below.

Potential Interferent		No Interference up to approximately
Plasma	Albumin	74.3 g/L
	Bilirubin	78 mg/dL
	Ditaurobilirubin	81 mg/dL
	Hemolysis	1081 mg/dL
	IgG	74.5g/L
	Lipemia	1668 mg/dL
Urine	Albumin	2.50 g/L
	Calcium	12.0 mg/dL
	Citrate	11.0 mg/dL
	Creatinine	88.4 mg/dL
	Hemolysis	1150 mg/dL
	IGG	1.10 g/L
	Magnesium	25.0 mg/dL
	Oxalate	1.50 mg/dL
	Phosphate	130 mg/dL
	Urea	1800 mg/dL
	Uric Acid	6.00 mg/dL
	Urobilinogen	1.13 mg/dL

ISE indirect Na

Endogenous interference

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Sodium electrode was determined on the **cobas pro** ISE analytical unit using human plasma, serum, and urine samples. A low (approximately 124 mmol/L) and high (approximately 151 mmol/L) samples were tested. A low concentration of 26.3 mmol/L and a high concentration of 188 mmol/L were tested for urine application. The summary of results is presented in the table below.

Potential Interferent		No Interference up to approximately
Plasma	Bilirubin	63 mg/dL
	Ditaurobilirubin	69 mg/dL
	Hemolysis	1137 mg/dL
	Lipemia	2326 mg/dL
Serum	Bilirubin	68.0 mg/dL
	Ditaurobilirubin	71.0 mg/dL
	Hemolysis	1144 mg/dL
	Lipemia	2206 mg/dL
Urine	Hemolysis	1141 mg/dL

Exogenous interference

The effect on quantitation of analyte in the presence of exogenous interfering substances was determined at 125 and 158 mmol/L for Serum and at 30 and 200 mmol/L for Urine applications.

Two sample pools, containing a low and high concentration of ISE indirect Na are used. These sample pools are divided into an appropriate number of aliquots. One aliquot is not spiked with the drugs and it is used as the reference sample for ISE indirect Na concentration. The ISE indirect Na concentration in the sample is determined with n=3 measurements on a **cobas pro** ISE analytical unit.

The other sample aliquots, with either the high or low ISE indirect Na concentrations, are spiked with the respective amount of drug. The ISE indirect Na concentration of the spiked aliquots are determined in triplicate and the mean of the triplicate determinations is compared to the ISE indirect Na concentration determined for the reference aliquot (mean of n=3).

Serum application	
Interference	**No Interference up to**
Acetaminophen (paracetamol)	200 mg/L
Acetylcysteine	1660 mg/dL
Acetylsalicylic acid	1000 mg/L
Ampicillin‑Na	1000 mg/L
Ascorbic acid	300 mg/L
Cefoxitin	2500 mg/L
Cyclosporin	5 mg/L
Doxycycline	50 mg/L
Heparin	5000 IU/L
Ibuprofen	500 mg/L
Intralipid	10000 mg/L
L‑Dopa	20 mg/L
Methyldopa	20 mg/L
Metronidazol	200 mg/L
Phenylbutazone	400 mg/L
Rifampicin	60 mg/L

Theophylline	100 mg/L

Urine application	
Interference	**No Interference up to**
Acetaminophen (paracetamol)	3000 mg/L
Acetylcysteine	10 mg/dL
Ascorbic acid	4000 mg/L
Gentamycin sulfate	400 mg/L
Ibuprofen	4000 mg/L
Levodopa	1000 mg/L
Methyldopa	2000 mg/L
Cefoxitin	12000 mg/L
Ofloxacine	900 mg/L
Phenazopyridine	300 mg/L
Salicyluric acid	6000 mg/L
Tetracycline	300 mg/L

Elecsys TSH

The serum samples may contain substances that could potentially interfere with the test. The following compounds were added to human serum samples with a low (approximately 0.462 µIU/mL), a mid (approximately 3.95 µIU/mL) and a high (approximately 7.54 µIU/mL) TSH concentration. One aliquot of each serum sample was spiked with the interfering substance, another aliquot was spiked with the same volume of isotonic NaCl solution (dilution pool). The interfering pool was then diluted into the dilution pool in 10 % increments. The recovery for each sample was calculated by comparison to the reference (unspiked) sample. None of the serum samples showed any deviation from the expected results. No interference was observed for these compounds at the levels indicated below.

Interference	Interference Substance
Biotin	1200 mg/dL
Lipemia (Intralipid)	2000 mg/dL
Hemoglobin	1000 mg/dL
Bilirubin	66 mg/dL
Rheumatoid Factor (RF)	1500 IU/mL
Immunoglobulin (IgG)	3.98 g/dL
Immunoglobulin (IgM)	0.730 g/dL

4.6. Analytical Specificity/Cross-Reactivity

The effect on quantitation of analyte in the presence of potential cross-reacting compounds using the Elecsys TSH was determined on the **cobas e** 801 analytical unit using a native human serum sample pool. For each potential cross-reacting compound a human serum sample with a low concentration level of TSH was tested. Results from these spiked serum samples were matched against the unspiked references and the % cross-reactivity was calculated. No cross reactivity was observed at the concentration tested.

Table 9: Summary of Cross-Reactivity

Cross-reactant	Concentration tested (µIU/mL)	Cross-reactivity %
hGH	10000000	0.000
hCG	50000000	0.000
LH	10000000	0.000
FSH	10000000	0.000

4.7. Exogenous Interferences – Drugs

The effect on quantitation of TSH in the presence of drugs was determined by comparing values obtained from samples spiked with 17 commonly and 13 specially used pharmaceutical compounds with the reference sample (unspiked). Two human serum samples (native serum pools) with analyte concentration approximately 0.5 and 8 µIU/mL were used and tested on the **cobas e**

801 analytical unit. The drug concentrations tested correspond at least to the three times maximum daily doses (or the one-time maximum daily dose, respectively). Drug interferences are measured based on recommendations given in CLSI guidelines EP07-ED3 and EP37-ED1 and other published literature. For all drugs tested, the specification of ± 10% of the reference value was met as each compound was found to be non-interfering at the drug concentration.

Table 10: Common Drugs

Potential interfering commonly used drugs	**Highest interferent concentration tested at which no significant interference was observed (mg/L)**
Acetylcysteine	150
Ampicillin - Na	75
Ascorbic acid	52.5
Cyclosporine	1.8
Cefoxitin	750
Heparin	3300 IU/mL
Levodopa	7.5
Methyldopa	22.5
Metronidazole	123
Phenylbutazone	321
Doxycycline	18
Acetylsalicylic acid	30
Rifampicin	48
Acetaminophen	156
Ibuprofen	219
Theophylline	60
Itraconazole	10

Table 11: Special Drugs

Drug	Highest interferent concentration tested at which no significant interference was observed (mg/L)
Amiodarone	200
Carbimazole	30
Fluocortolone	100
Hydrocortisone	200
Iodide	0.2
Levothyroxine	0.25
Liothyronine	0.075
Methimazole	80
Octreotide	0.3
Prednisolone	100
Propranolol	240
Propylthiouracil	300
Perchlorate	2000

4.8. Method Comparison to Predicate

Glucose HK

A method comparison was performed using the Glucose HK Gen.3 (GLUC3) assay (**c 503**, Y) and the predicate, Glucose HK Gen.3 (GLUC3) assay on the **cobas c** 501 analyzer(X) to assess the bias between the two analytical units in two different cores. A total of 74 native human serum samples, 67 native human urine samples and 75 native CSF samples were measured in singlicate on the **cobas c** 503 analyzer in one run covering the entire measuring range.

A summary of results is presented in the table below.

Table 12: Summary of Method Comparison

Method	Sample Type (number of samples)	Passing/Bablok (Slope & Intercept) and correlation (Kendall tau (t))	Linear Regression (Slope & Intercept) and correlation (Pearson (r))	Sample concentration range (mg/dL)
cobas c 503 vs. cobas c 501	Serum (74)	1.000x – 0.0200 t = 0.987	0.997x – 0.00454 r = 1.000	5.8 – 725.4
cobas c 503 vs cobas c 501	Urine (67)	0.995x – 0.0447 t = 0.982	0.995x – 0.0402 r = 1.000	3.1 - 736.2
cobas c 503 vs cobas c 501	CSF (75)	1.000x + 0.00400 t = 0.957	1.001x + 0.0287 r = 0.999	3.6 - 734.4

ISE indirect Na

A method comparison was performed using the ISE indirect Na assay (on **cobas pro** ISE in **cobas pro** core, Y) and the predicate device, **cobas c** 501 ISE, X) to assess the bias between the two test systems. Additionally, the results of the candidate test system were compared against flame photometry. A total of 120 human Lithium heparin plasma samples for **cobas pro** ISE versus **cobas c** 501 ISE, 118 human Lithium heparin plasma for **cobas pro** ISE vs Flame Photometer, 120 human serum for **cobas pro** ISE vs c 501 ISE, 120 human serum versus Flame Photometer and 120 human urine were measured in singleton on the **cobas pro** ISE analyzer in one run covering the entire measuring range.

Table 13: Summary of Method Comparison

cobas pro ISE vs	Sample Type (number of samples)	Passing/Bablok (Slope & Intercept) and correlation (Pearson (r))	Sample concentration range (mmol/L)
cobas c 501 ISE	Plasma (120)	1.003x – 1.72 r = 1.000	84.2-177
Flame Photo.	Plasma (118)	1.031x – 4.12 r = 0.997	80.4-175
cobas c 501 ISE	Serum (120)	1.027x – 4.38 r = 1.000	84.4 -175
Flame Photo.	Serum (120)	1.016x – 1.11 r = 0.996	81.3 -174
cobas c 501 ISE	Urine (120)	1.019x – 2.90 r = 1.000	25.5-241
Flame Photo.	Urine (120)	0.993x – 2.46	22.5-249

		r = 1.000	

Elecsys TSH

A method comparison was performed using the Elecsys TSH assay (on **cobas e** 801 in **cobas pro** core, Y) and the Elecsys TSH assay (on **cobas e** 801 in **cobas** 8000 core, X) to assess the bias between the two test systems. A total of 138 samples (129 native human serum samples and 9 diluted human serum samples, single donors as well as pools diluted) were measured in singleton on each **cobas e** 801 analytical unit in one run covering the entire measuring range.

Table 14: Summary of Method Comparison (Passing/Bablok)

N	138
Range (µIU/mL)	0.006 – 97.8
Slope (LCL / UCL)	1.018 (1.004 / 1.025)
Intercept (µIU/mL) (LCL / UCL)	-0.0018 (-0.0040 /- 0.0001)
Correlation coefficient, Pearson (r) Correlation coefficient, Kendall (tau)	0.999 0.977
Bias at 0.27 µIU/mL (LCL / UCL) Bias at 4.2 µIU/mL (LCL / UCL)	1.2 % (0.0%/ 1.8%) 1.8% (0.4% / 2.5%)

4.9. Sample Matrix Comparison

Glucose HK

The effect on quantitation of analyte in the presence of anticoagulants with the Glucose HK Gen.3 assay was determined by comparing values obtained from samples (native human serum samples, single donors drawn into serum/gel separation tubes and K_2-EDTA, Li-Heparin, NaF/K-Oxalate NaF/Na_2-EDTA, NaF/Citrate/Na_2-EDTA and KF/Na_2-EDTA plasma tubes).

The recovery of analyte values in the presence of anticoagulants with the Glucose HK Gen.3 assay was determined on the **cobas c** 503 analytical unit by comparing values obtained from samples drawn into serum and plasma collection tubes. The recovery of each plasma sample to the matching

serum sample was calculated. At least 39 serum/plasma pairs were tested for each kind of anticoagulant in single determination.

Table 15: Summary of Matrix Comparison

Matrix Comparison (Passing/Bablok)		
Serum vs Serum Tube with Separation Gel	N	39
	Range	3.6 – 694.8 mg/dL
	Slope	1.000
	Intercept	0.00500
	Correlation coefficient r	0.999
Serum tube vs K_2EDTA Plasma Tube	N	52
	Range	3.6 – 694.8 mg/dL
	Slope	1.005
	Intercept	-0.0108
	Correlation coefficient r	0.998
Serum tube vs Lithium Heparin Plasma Tube	N	51
	Range	3.6 – 694.8 mg/dL
	Slope	1.007
	Intercept	-0.0274
	Correlation coefficient r	0.998
Serum tube vs NaF/K-Oxalate Plasma Tube	N	50
	Range	3.6 – 694.8 mg/dL
	Slope	1.006
	Intercept	-0.0100
	Correlation coefficient r	0.998
Serum tube vs NaF/ Na_2-EDTA Plasma Tube	N	50
	Range	3.6 – 694.8 mg/dL
	Slope	1.020
	Intercept	-0.0241
	Correlation coefficient r	0.998
Serum tube vs NaF/Citrate/ Na_2-EDTA Plasma Tube	N	50
	Range	3.6 – 694.8 mg/dL
	Slope	1.035
	Intercept	-0.104

Matrix Comparison (Passing/Bablok)		
	Correlation coefficient r	0.998
Serum tube vs KF/Na_2-EDTA Plasma Tube	N	52
	Range	3.6 – 694.8 mg/dL
	Slope	0.996
	Intercept	-0.0367
	Correlation coefficient r	1.000

ISE indirect Na

The effect on quantitation of analyte in the presence of anticoagulants with the ISE indirect Na was determined by comparing values obtained from samples drawn into serum and Li-Heparin plasma tubes. A total of 50 serum/ Li-Heparin plasma pairs per sample material were tested in singleton with one reagent lot on one **cobas pro** ISE analytical unit. Data were evaluated using a regression analysis according to Passing/Bablok.

Table 16: Summary of Matrix Comparison

Matrix Comparison (Passing/Bablok)		
Serum/Li-Heparin	N	50
	Range	83.1 – 174 mmol/L
	Slope	1.015
	Intercept	-2.69
	Correlation coefficient r	0.998

Elecsys TSH

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys TSH immunoassay was determined by comparing values obtained from samples (native human serum samples, single donors as well as pools) drawn into serum and Li-Heparin, K_2-EDTA, K_3-EDTA plasma tubes. A minimum of 56 serum/plasma pairs per sample material were tested in singleton with one reagent lot on one **cobas e** 801 analyzer. Data were evaluated using a regression analysis according to Passing/Bablok. Serum separation tubes from 3 separate manufacturers and blood from five donors were used. Measurements were performed in duplicate with one reagent lot and

evaluated on the basis of recovery relative to the serum / plasma tube without separating gel (reference).

Table 17: Summary of Matrix Comparison

Matrix Comparison (Passing/Bablok)		
Serum/Li-Heparin Plasma	N	50
	Range	0.006 – 97.1 µIU/mL
	Slope	0.982
	Intercept	0.0002 µIU/mL
	Correlation coefficient r	0.999
	Bias at 0.2 µIU/mL	-1.7 %
	Bias at 2.5 µIU/mL	-1.8 %
Serum/K2-EDTA Plasma	N	51
	Range	0.006 – 97.1 µIU/mL
	Slope	0.977
	Intercept	-0.0015 µIU/mL
	Correlation coefficient r	1.000
	Bias at 0.2 µIU/mL	-2.8 %
	Bias at 2.5 µIU/mL	-2.3 %
Serum/K3-EDTA Plasma	N	51
	Range	0.006 – 97.1 µIU/mL
	Slope	0.971
	Intercept	-0.0123 µIU/mL
	Correlation coefficient r	1.000
	Bias at 0.2 µIU/mL	-7.5 %
	Bias at 2.5 µIU/mL	-3.2 %

4.10. Stability

The stability data for Glucose HK Gen.3, ISE indirect Na and Elecsys TSH was provided in k061048, k060373, and k190773 respectively. The stability data supports Roche Diagnostic's claims as reported in the package inserts.

4.11. Conclusion

Based on the analytical testing results and acceptance performance characteristics including sensitivity, precision, specificity, interference and method comparison of the device, it is concluded that Glucose, ISE indirect Na, TSH and the **cobas pro** integrated solutions are substantially equivalent to the predicate devices.