September 16, 2022

Roche Diagnostics
Noel Mencias
Program Manager, Regulatory Affairs
9115 Hague Road
Indianapolis, IN 46250

Re: K220134
Trade/Device Name: Glucose HK Gen.3, ISE indirect Na for Gen.2, Elecsys TSH, ONLINE DAT Methadone II, cobas pure integrated solutions
Regulation Number: 21 CFR 862.1345
Regulation Name: Glucose test system
Regulatory Class: Class II
Product Code: CFR, JGS, JLW, DJR, JJE
Dated: July 1, 2022
Received: July 5, 2022

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 (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,

Paula V. Caposino, Ph.D.
Acting 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.

Submission Number *(if known)*

K220134

Device Name

cobas pure integrated solutions;
Glucose HK Gen.3;
ISE indirect Na for Gen.2;
ONLINE DAT Methadone II;
Elecsys TSH

Indications for Use *(Describe)*

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

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 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.

Methadone II (MDN2) is an in vitro diagnostic test for the qualitative and semiquantitative detection of methadone in human urine on Roche/Hitachi cobas c systems at a cutoff concentration of 300 ng/mL. Semiquantitative test results may be obtained that permit laboratories to assess assay performance as part of a quality control program. Semiquantitative assays are intended to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as gas chromatography/mass spectrometry (GC-MS).

Elecsys TSH is an 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 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.

Contact Details 21 CFR 807.92(a)(1)

Applicant Name	Roche Diagnostics
Applicant Address	9115 Hague Road Indianapolis IN 46250 United States
Applicant Contact Telephone	463-336-2546
Applicant Contact	Mr. Noel Mencias
Applicant Contact Email	noel.mencias@roche.com

Device Name 21 CFR 807.92(a)(2)

Device Trade Name	Glucose HK Gen.3; ISE indirect Na for Gen.2; ONLINE DAT Methadone II; Elecsys TSH; cobas pure integrated solutions
Common Name	GLUC3; ISE Na; MDN2; TSH; cobas pure integrated solutions
Classification Name	Hexokinase, glucose; Electrode, ion specific, sodium; enzyme immunoass
Regulation Number	862.1345; 862.1665; 862.3620; 862.1690; 862.2160
Product Code	CFR; JGS; DJR; JLW; JJE

Legally Marketed Predicate Devices 21 CFR 807.92(a)(3)

Predicate #	Predicate Trade Name (Primary Predicate is listed first)	Product Code
K191899	cobas pro integrated solutions	JJE
K191899	Glucose HK Gen.3	CFR
K191899	ISE indirect Na for Gen.2	JGS
K021505	ONLINE DAT Methadone II	DJR
K191899	Elecsys TSH	JLW

Device Description Summary 21 CFR 807.92(a)(4)

cobas pure integrated solutions
The cobas pure integrated solutions is a fully automated, random-access, software controlled system intended for in vitro quantitative and qualitative analysis of analytes in body fluids. It will typically be used in low to mid throughput clinical laboratories. The system consolidates clinical chemistry, homogenous and heterogeneous immunoassays as well as electrolyte testing within one workplace. The cobas pure integrated solutions consists of a clinical chemistry analytical unit (cobas c 303) with an integrated ISE analytical unit, an immunoassay analytical unit (cobas e 402) and a core unit.

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.

ISE indirect Na for Gen. 2
The ISE analytical unit 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.

ONLINE DAT Methadone II
The Methadone assay is based on the kinetic interaction of microparticles in a solution (KIMS) as measured by changes in light transmission. In the absence of sample drug, soluble drug conjugates bind to antibody-bound microparticles, causing the formation of particle aggregates. As the aggregation reaction proceeds in the absence of sample drug, the absorbance increases.

When a urine sample contains the drug in question, this drug competes with the drug derivative conjugate for microparticle-bound antibody. Antibody bound to sample drug is no longer available to promote particle aggregation, and subsequent particle lattice formation is inhibited. The presence of sample drug diminishes the increasing absorbance in proportion to the concentration of drug in the sample. Sample drug content is determined relative to the value obtained for a known cutoff concentration of drug.

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.
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. It is intended for use on the cobas e immunoassay analyzers.

Intended Use/Indications for Use 21 CFR 807.92(a)(5)

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

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.

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Methadone II (MDN2) is an in vitro diagnostic test for the qualitative and semiquantitative detection of methadone in human urine on Roche/Hitachi cobas c systems at a cutoff concentration of 300 ng/mL. Semiquantitative test results may be obtained that permit laboratories to assess assay performance as part of a quality control program. Semiquantitative assays are intended to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as gas chromatography/mass spectrometry (GC-MS).

Elecsys TSH is an 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 cobas e immunoassay analyzers.

Indications for Use Comparison 21 CFR 807.92(a)(5)

Indications for use are the same as the predicate device.

Technological Comparison 21 CFR 807.92(a)(6)

The cobas pure integrated solutions is a next generation of the cobas 6000 analyzer series (cobas 6000) which was cleared under K060373. The cobas pro integrated solutions, cleared in K191899, is the first of the next generation platforms and the predicate of cobas pure integrated solution. The cobas pure integrated solutions consists of a clinical chemistry analytical unit (cobas c 303) with an integrated ISE analytical unit, an immunoassay analytical unit (cobas e 402) and a core unit. The clinical chemistry (CC) and the ISE analytical units are part of the existing Roche/Hitachi/cobas c family of analyzers and the immunoassay (IM) analyzer are part of the existing Elecsys family of analyzers. These share technological characteristics with the predicate cobas pro integrated solutions, modified for lower throughput. The reagents and calibrators/controls to be applied on cobas pure integrated solutions will be existing devices already cleared on existing Roche/Hitachi cobas c or Elecsys instrumentation.

The representative reagents Glucose HK Gen.3, ISE indirect Na for Gen.2, ONLINE DAT Methadone II, and Elecsys TSH share the technological characteristics of their predicate devices.

Non-Clinical and/or Clinical Tests Summary & Conclusions 21 CFR 807.92(b)

Glucose HK Gen.3
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 same cobas c 303 analytical unit using 1 lot of reagent. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated.

The linearity study was performed according to CLSI guideline EP06-A on one cobas c 303 analyzer.

The Limit of Blank (LoB) of the Glucose HK Gen.3 assay on the cobas c 303 analytical unit assay was 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 Glucose HK Gen.3 assay on the cobas c 303 analytical unit was 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 Glucose HK Gen.3 assay was 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 20%.

Endogenous Interference studies were conducted to determine the effects of interference by hemoglobin, lipemia (Intralipid), albumin, Immunoglobulin (IgG) and bilirubin/ditaurobilirubin on the Glucose HK Gen.3 were determined on the cobas c 303.

Drug Interference studies were conducted to evaluate drugs for potential interference with Glucose Gen.3 HK assay measured on the cobas c 303 analytical unit.

Method Comparison experiments were performed for all sample types using the Glucose HK Gen.3 assay on the cobas c 303 versus the Glucose HK Gen.3 assay on the cobas c 503.

Matrix Comparison studies were performed to support the use of several different anticoagulant tube types.

On-board reagent stability was verified on the cobas c 303 for the specified time frame: 26 weeks on board.

Post Dilution Check experiments were run across the measuring range to verify the automatic rerun function of the analytical unit.

Recovery in Controls on cobas c 303 were tested.

ISE indirect Na for Gen.2
Precision experiments were performed in accordance with CLSI guideline EP05-A3. One run per day for ≥ 21 days with two parts, two aliquots per part were performed on the same cobas c 303 ISE analytical unit using one reagent lot. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated.

The linearity study was conducted to demonstrate that measurements across the claimed measuring range for each parameter are linear. The study was performed according to CLSI guideline EP06-A.

The Limit of Blank (LoB) of the ISE indirect Na for Gen. 2 assay on the cobas c 303 ISE analytical unit was 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 for Gen. 2 assay on the cobas c 303 ISE analytical unit was 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 ISE indirect Na for Gen. 2 assay was 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%.

The effects of interference by endogenous substances bilirubin, ditaurobilirubin, hemolysis and lipemia (Intralipid) on the ISE Na test system were determined on the cobas c 303 ISE analyzer using pooled human plasma and serum samples spiked with varying levels of interferent.

A Drug Interference study was conducted to evaluate drugs for potential interference with ISE indirect Na for Gen.2 assay measured on the cobas c 303 ISE analytical unit.
Method Comparison experiments were performed for all sample types using ISE indirect Na for Gen2. on the cobas c 303 ISE versus ISE indirect Na for Gen2. on cobas pro ISE and flame photometry to assess the bias.

The effect of the presence of anticoagulants on analyte recovery was determined by matrix comparison on one cobas c 303 ISE, obtained from samples drawn into Li-Heparin Plasma and Serum collection tubes.

A study verifying calibration frequency was performed.

Post Dilution Check experiments were run across the measuring range to verify the automatic rerun function of the cobas c 303 ISE analytical unit.

Recovery in controls were measured on the cobas c 303 ISE analytical unit.

ONLINE DAT Methadone II
Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days).

To test endogenous interference, interfering substances were added to urine containing methadone at - 25 % and + 25 % of the cutoff level at specified concentrations. Samples were tested on the cobas c 303 analytical unit with the ONLINE DAT Methadone II assay.

The effects of drug interference were conducted on one cobas c 303. Aliquots of the drug in a human urine containing methadone at the control level concentrations were prepared. The compounds were added at the specified concentrations to pooled human urine containing methadone at a concentration of 225 ng/mL (negative control level) or 375 ng/mL (positive control level). For each compound, negative results relative to the 300 ng/mL cutoff were obtained for the samples containing methadone at a concentration of 225 ng/mL (negative control level) and positive results were obtained for the samples containing methadone at a concentration of 375 ng/mL (positive control level), with the Methadone II assay.

Cross Reactivity studies were conducted by generating inhibition curves and determining the approximate quantity of each compound that is equivalent in assay reactivity to a 300 ng/mL assay cutoff.

Method Comparison studies were conducted with the Methadone II assay on the cobas c 303 analyzer relative to GC-MS and relative to cobas c 503.

Recovery in Controls on cobas c 303 were tested.

Elecsys TSH
Precision measurements were conducted to evaluate repeatability (within-run precision) and the intermediate precision (within-laboratory precision) according the CLSI guideline EP05-A3.
Linearity of the Elecsys TSH assay was assessed on the cobas e 402 Immunoassay analyzer according to CLSI EP06-A.

LoB of the Elecsys TSH on the cobas e 402 analyzer was determined according to CLSI EP17-A2. Limit of Blank determines the highest

observed measurement values for samples free of analyte. The Limit of Blank was determined as the 95th percentile of measurements of blank samples.

LoD of the Elecsys TSH assay on the cobas e 402 Immunoassay analyzer has been determined according to CLSI EP17-A2. The LoD was determined as the lowest amount of analyte in a sample that can be detected with 95% probability.

The LoQ of the Elecsys TSH was determined on the cobas e 402 analyzer according to CLSI Guideline 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 20%.

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys TSH was determined on the cobas e 402 immunoassay analyzer using human serum samples (native serum pools).

The effect on quantitation of analyte in the presence of drugs was determined by comparing values obtained from samples spiked with commonly and specially used pharmaceutical compounds with the reference sample (unspiked).

The effect on quantitation of analyte in the presence of potential cross-reacting compounds using the Elecsys TSH was determined on the cobas e 402 immunoassay analyzer using a native human serum sample pool.

On-board reagent stability for the Elecsys TSH assay was tested on one cobas e 402 immunoassay analyzer.

A method comparison was performed using the Elecsys TSH updated assay (candidate device, cobas e 402 in cobas pure integrated solution, Y) and the Elecsys TSH current assay (predicate device, cobas e 801 in cobas pro integrated solution, X) to assess the bias between the two assays.

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, Li-Heparin, K2-EDTA, K3-EDTA plasma tubes.

The high-dose hook effect of the Elecsys TSH assay was assessed on the cobas e 402 analyzer.

The analytical performance data for all representative assays meet specifications and support the substantial equivalence of Glucose HK Gen.3, ISE indirect Na for Gen.2, ONLINE DAT Methadone II, Elecsys TSH, and cobas pure integrated solutions to the predicate devices.