April 7, 2023

Roche Diagnostics
Bin Sun
Regulatory Affairs Program Manager
9115 Hague Road
Indianapolis, IN 46250

Re: K220456
Trade/Device Name: Elecsys FT4 IV
Regulation Number: 21 CFR 862.1695
Regulation Name: Free Thyroxine Test System
Regulatory Class: Class II
Product Code: CEC
Dated: December 8, 2022
Received: December 9, 2022

Dear Bin Sun:

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 -S
Digitally signed by Paula V. Caposino -S
Date: 2023.04.07 15:49:39 -04'00'

Paula 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.

510(k) Number *(if known)*
K220456

Device Name
Elecsys FT4 IV

Indications for Use *(Describe)*
Assay for the in vitro quantitative determination of free thyroxine in human serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of thyroid disease.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on the 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.

K220456 Elecsys FT4 IV
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.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Bin Sun Phone: (317) 292-3781 Email: bin.sun.bs2@roche.com
Date Prepared	April 6, 2023
Proprietary Name	Elecsys FT4 IV
Common Name	Free thyroxine
Classification Name	Radioimmunoassay, Free thyroxine test system
Product Codes, Regulation Numbers	CEC, 21CFR862.1695
Predicate Devices	Elecsys FT4 II (K131244)
Establishment Registration	Roche Diagnostics GmbH Mannheim, Germany: 9610126 Roche Diagnostics GmbH Penzberg, Germany: 9610529 Roche Diagnostics Indianapolis, IN United States: 1823260

1. DEVICE DESCRIPTION

The Elecsys FT4 IV immunoassay a fourth generation FT4 assay by Roche Diagnostics for the for the in vitro quantitative determination of free thyroxine in human serum and plasma. It is intended for use on the cobas e immunoassay analyzers. The cobas e family of analyzers uses electrochemiluminescence immunoassay "ECLIA" technology. The assay is an 18 minute assay utilizing a competition principle using a monoclonal antibody which is specifically directed against free thyroxine. Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration against the master curve for that reagent lot.

1.1. Reagents

The reagent working solutions include:

Rackpack (kit placed on analyzer)

- M: Streptavidin-coated microparticles
- R1: Anti-T4-Ab~$Ru(bpy)_3^{2+}$
- R2: T4~biotin

2. INDICATIONS FOR USE

Assay for the in vitro quantitative determination of free thyroxine in human serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of thyroid disease.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e** immunoassay analyzers.

3. TECHNOLOGICAL CHARACTERISTICS

The following tables compare the Elecsys FT4 IV with its predicate device, Elecsys FT4 II assay (k131244).

Item	**Predicate (Elecsys FT4 II, k131244)**	**Candidate Device (Elecsys FT4 IV)**
Proprietary name	Elecsys FT4 II	Elecsys FT4 IV

Item	Predicate (Elecsys FT4 II, k131244)	Candidate Device (Elecsys FT4 IV)
Indications for Use	The Elecsys FT4 II assay is for the in vitro quantitative determination of free Thyroxine in human serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of thyroid diseases. **The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers**	The Elecsys FT4 IV assay is for the in vitro quantitative determination of free Thyroxine in human serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of thyroid disease. **The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.**
Test Principle	The Elecsys FT4 II assay is a two-step competitive immunoassay with streptavidin microparticles and electrochemiluminescence detection system.	No change
Technology	ECLIA	No change
Test format	Competitive	No change
Test type	Quantitative	No change
Application time	18 min	No change
Assay protocol	1st Incubation: R1+sample 2nd incubation: Addition of R2 + streptavidin-coated microparticles (beads)	No change
Sample type	Undiluted human serum and undiluted plasma treated with Li-heparin, K_2-EDTA and K_3-EDTA	No change
Pipetting volume sample	15 µL	No change
Pipetting volume beads	35 µL	No change
Pipetting volume R1	75 µL	No change
Pipetting volume R2	75 µL	No change
Handling of R1 and R2	Liquid, ready to use	No change
Buffer composition R1	phosphate buffer 100 mmol/L	No Change
	-	Anti-Biotin Antibody; specific for free, unconjugated biotin ("scavenger antibody"). MAK<Biotin>rK-21E12-IgG
Antibodies used in R1	Ruthenylated polyclonal T4-specific sheep antibody PAB<T4>S-Fab-sRu	Ruthenylatedmonoclonal T4-specific rabbit antibody. MAB<T4>rK-38F8-Fab-sRu
Buffer composition R2	phosphate buffer 100 mmol/L	No Change
	D-Biotin	N-Biotinylsarcosine (Biotin-derivate)

Item	Predicate (Elecsys FT4 II, k131244)	Candidate Device (Elecsys FT4 IV)
Biotinylated component in R2	T4(OSu)-bis-DADOO-Bi	No change
Biotin Tolerance	< 20 ng/mL	≤ 1200 ng/mL
SA interference elimination	Yes	Improved, addition of Streptavidin rec. Mutein Polymer
Measuring range	0.101-7.77 ng/dL (1.3-100 pmol/L)	No change
Analytical Sensitivity	Limit of Blank = 0.03 ng/dL (0.4 pmol/L) Limit of Detection = 0.05 ng/dL (0.6 pmol/L) Limit of Quantitation = 0.101 ng/dL (1.3 pmol/L)	Limit of Blank = 0.02 ng/dL (0.3 pmol/L) Limit of Detection = 0.04 ng/dL (0.5 pmol/L) Limit of Quantitation = 0.101 ng/dL (1.3 pmol/L)
Calibrators	FT4 II CalSet	CalSet FT4 IV
Control material	PreciControl Universal	No Change

4. NON-CLINICAL PERFORMANCE EVALUATION

Non-clinical performance evaluation for Elecsys FT4 IV executed with the study briefly summarized.

4.1. Precision

4.1.1. Repeatability and Intermediate Precision

Precision measurements were conducted for both 21 days and 5 days with the Elecsys FT4 IV assay to evaluate repeatability (within-run precision) and intermediate precision (within-laboratory precision) according the CLSI guideline EP05-A3. All predefined acceptance criteria was met for the precision experiments. The results are summarized below:

		Repeatability		Intermediate precision	
Sample	Mean ng/dL (pmol/L)	SD ng/dL (pmol/L)	CV %	SD ng/dL (pmol/L)	CV %
Human serum 1	0.124 (1.59)	0.003 (0.040)	2.5	0.007 (0.089)	5.6
Human serum 2	0.515 (6.63)	0.006 (0.071)	1.1	0.012 (0.153)	2.3

		Repeatability		Intermediate precision	
Sample	Mean ng/dL (pmol/L)	SD ng/dL (pmol/L)	CV %	SD ng/dL (pmol/L)	CV %
Human serum 3	0.979 (12.6)	0.010 (0.133)	1.1	0.019 (0.248)	2.0
Human serum 4	1.82 (23.4)	0.017 (0.222)	1.0	0.031 (0.402)	1.7
Human serum 5	3.50 (45.0)	0.043 (0.558)	1.2	0.074 (0.957)	2.1
Human serum 6	6.85 (88.2)	0.117 (1.51)	1.7	0.181 (2.33)	2.6
PC[c)] Universal 1	1.17 (15.1)	0.010 (0.131)	0.9	0.021 (0.265)	1.7
PC Universal 2	3.09 (39.8)	0.037 (0.482)	1.2	0.064 (0.824)	2.1

4.1.2. Lot-to-lot reproducibility

Lot-to-lot reproducibility was performed for the Elecsys FT4 IV assay using three reagent lots according the CLSI guideline EP05-A3. All predefined acceptance criteria was met for the lot-to-lot reproducibility experiment.

4.2. Analytical Sensitivity

4.2.1. Limit of Blank (LoB)

Experimental Design included three reagent lots evaluated on one **cobas e** 411 analyzer, six runs over three or more days with one blank sample with ten replicates per run. The zero-level (blank) sample used was fT4 depleted human serum sample pool. In total, 60 determinations for analyte free samples have been obtained. The LoB was calculated according to CLSI EP17-A2. The LoB claim in the labeling will be set to 0.02 ng/dL (0.3 pmol/L).

4.2.2. Limit of Detection (LoD)

Experimental Design included three reagent lots evaluated on one **cobas e** 411 analyzer, six runs over three or more days with five samples with two replicates/sample/run. The five samples were low-level human serum sample pools (diluted). A pooled estimate of the precision (SD total) for the 5 low-level samples was calculated. The LoD was calculated according to CLSI EP17-A2. The LoD claim in the labeling will be set to 0.04 ng/dL (0.5 pmol/L).

4.2.3. Limit of Quantitation (LoQ)

The LoQ is defined as the lowest concentration of analyte that can be reproducibly measured with an intermediate precision CV of no more than 20%. Experimental Design included three reagent lots evaluated on one **cobas e** 411 analyzer, one run per day over five days. Five replicates per each sample per run with at least five low level samples of serum and 25 replicates/sample/reagent lot. The LoQ was calculated according to CLSI EP17-A2. The LoQ claim in the labeling will be set to 0.101 ng/dL (1.3 pmol/L).

4.3. Linearity/Assay Reportable Range

Linearity of the Elecsys FT4 IV assay was assessed using human serum samples on the **cobas e** 411 Immunoassay Analyzer according to CLSI EP6-Ed2.

The serum samples spiked by T4 (sample High) and diluted by fT4 depleted human serum (sample Blank) are used to prepare dilutions series. Three individual human serum samples with an analyte concentration above the upper limit of the measuring range and sample Blank with known of zero are mixed to prepare the dilution series. 13 concentrations (levels) cover the measuring range were prepared. The concentration ranges of the samples cover the entire measuring range of the assay. Samples were assayed in 4-fold determination within a single run. SD and CV were calculated for each 4-fold determination on 1 lot of reagent. The linearity data is analyzed using first-order Weight Least Squares regression (WLS) without intercept according to CLSI EP06-Ed2.

Linearity was confirmed in the range of 0.098-8.13 ng/dL (1.26-105 pmol/L), and a measuring range of 0.101-7.77 ng/dL (1.3-100 pmol/L) will be claimed in the labeling.

4.4. Human Anti-Mouse Antibodies (HAMA)

Not Applicable (no mouse antibodies used)

4.5. Endogenous Interferences

Nine endogenous substances were evaluated for potential interference with the Elecsys FT4 IV assay on the **cobas e** 411 analyzer according the CLSI guideline EP07-A3. All predefined acceptance criteria was met, and the proposed labeling claims for each endogenous substance can be found below:

Compound	**Concentration tested**
Bilirubin	≤ 701 µmol/L or ≤ 41 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 7 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1 g/dL
Albumin	≤ 6.3 g/dL

4.6. Analytical Specificity/Cross-Reactivity

A cross-reactivity study was conducted with Elecsys FT4 IV on the **cobas e** 411 analyzer to evaluate the potential cross-reacting compounds using human serum samples (native human single donor sera). For each potential cross-reacting compound two human serum samples with a low (approximately 1.5 ng/dL or 19.4 pmol/L) and slightly elevated (approximately 5 ng/dL or 64.5 pmol/L) concentration level of FT4 were tested. The results are summarized below:

Cross-reactant	Concentration tested ng/dL	Cross-reactivity %
L-T3	50000	0.005

Cross-reactant	Concentration tested ng/dL	Cross-reactivity %
D-T3	50000	0.003
rT3	190000	0.002
3-iodo-L-tyrosine	10000000	0.000
3,5-diiodo-L-tyrosine	10000000	0.000
3,3',5-triiodothyroacetic acid	100000	0.000
3,3',5,5'-tetraiodothyroacetic acid	100000	0.003

4.7. Exogenous Interferences – Drugs

An exogenous interference study was conducted to evaluate 17 commonly and 15 specially used pharmaceutical compounds for potential interference with the Elecsys FT4 IV assay on the **cobas e** 411 analyzer. No significant interference was found with the highest concentration tested listed in the table below:

Common therapeutic drugs	**Concentration tested** **µg/mL**
Acetylcysteine	150.0
Ampicillin	75.0
Ascorbic Acid	52.5
Cyclosporine	1.80
Cefoxitin	750
Heparin	3300 IU/L
Itraconazole	15.0
Levodopa	7.50
Methyldopa	22.5
Metronidazole	123.0
Phenylbutazone	80.0

Common therapeutic drugs	Concentration tested µg/mL
Doxycycline	18.0
Acetylsalicylic Acid	30.0
Rifampicin	48.0
Acetaminophen	156.0
Ibuprofen	109.0
Theophylline	60.0

The drugs Furosemide, Carbamazepine, Phenytoin and Levothyroxine Sodium (L-T4, synthetic levothyroxine) caused elevated FT4 findings at the daily therapeutic dosage level. For all other special thyroid drugs tested the specification was met as each compound was found to be non-interfering at the stated drug concentrations.

The results are summarized below:

Drug	Concentration tested µg/mL
Carbimazole	18
Thiamazole	80
Propylthiouracil	300
Perchlorate	600
Propranolol	120
Amiodarone	200
Prednisolone	100
Hydrocortisone	200
Octreotide	0.3
Furosemide	3.5
Liothyronine	0.02
Potassium iodide (SSKI)	150

Drug	Concentration tested µg/mL
Lithium	540
Phenytoin	13.5
Carbamazepine	9

4.8. Sample Matrix Comparison

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys FT4 IV immunoassay was determined by comparing values obtained from samples (native single donors and pools as well as spiked or diluted samples) drawn into Serum, Li-Heparin, K2-and K3-EDTA plasma primary tubes. All predefined acceptance criteria was met, supporting the labeling claim that serum, Li-Heparin, K2-EDTA and K3-EDTA plasma are acceptable sample types.

4.9. Method Comparison to Predicate

A method comparison was performed with the Elecsys FT4 II assay (predicate device) and the Elecsys FT4 IV assay, using a total of 121serum samples on the **cobas e** 411 analyzer using one lot of the Elecsys FT4 II assay and one lot of the FT4 IV assay covering the entire measuring range. The sample concentrations were between 0.13 and 7.68 ng/dL (1.65 and 98.8 pmol/L) for the reference method. The results can be found below (ng/dL):

Passing Bablok

$y = 1.03x - 0.025$

$\tau = 0.967$

Linear regression

$y = 1.04x - 0.034$

$r = 0.999$

4.10. Reagent Stability

To test reagent stability, two studies completed, including:

- Study 1: Reagent stability after first opening at 2-8°C (84 days)
- Study 2: On board reagent stability (28 days)

4.10.1. Reagent Stability After First Opening

Reagent stability after first opening for the Elecsys FT4 IV assay was tested on one **cobas e** 411 analyzer. Elecsys FT4 IV reagent kits can be used after first opening for up to 84 days when stored at 2-8°C.

4.10.2. Reagent On-board stability (28 days)

On-board reagent stability for the Elecsys FT4 IV assay was tested on one **cobas e** 411 analyzer. Elecsys FT4 IV reagent kits can be stored on-board the analyzers for up to 28 days (4 weeks).

4.11. Calibration Stability

To test calibration stability, two studies were completed, including:

- Study 1. Lot calibration stability
- Study 2. On-board calibration stability

4.11.1. Lot calibration study

Lot calibration frequency for the Elecsys FT4 IV assay was tested on one **cobas e** 411 analyzer. Calibrations of an Elecsys FT4 IV reagent lot is recommended every 28 days (1 month) when using the same reagent lot.

4.11.2. On-board Calibration Stability

Reagent on-board calibration frequency for Elecsys FT4 IV assay was tested on one **cobas e** 411 analyzer. Elecsys FT4 IV reagent kits can be stored on board of the analyzers for up to 7 days without a new calibration.

5. EXTERNAL (CLINICAL) TESTING

Not Applicable

6. CLINICAL PERFORMANCE EVALUATION

Not Applicable

7. EXPECTED VALUES/REFERENCE RANGE

A Reference Range study was performed in order to determine the specific reference intervals for Elecsys FT4 IV on the **cobas e** 411 immunoassay analyzer from health donors in the United States under routine laboratory conditions according to CLSI EP28-A3c. Serum samples from apparently healthy donors in the United States were obtained from a commercial vendor according to the inclusion and exclusion criteria. One clinical laboratory was contracted to measure samples with Elecsys FT4 IV assay on the **cobas e** 411 analyzer.

The calculated 95% reference range corresponds to the 2.5th and 97.5th percentiles of results obtained from 150 apparently healthy subjects is 0.92 – 1.68 ng/dL (11.9 – 21.6 pmol/L). The results are summarized below:

2.5th percentile	**95 % CI of the 2.5th percentile**	**97.5th percentile**	**95 % CI of the 97.5th percentile**	**Unit**
0.92	0.81-0.96	1.68	1.51-2.00	ng/dL
11.9	10.4-12.3	21.6	19.4-25.8	pmol/L

8. ADDITIONAL INFORMATION

The Elecsys FT4 IV is intended to be used with the following calibrators and controls:

- FT4 IV CalSet
- PreciControl Universal

FT4 IV CalSet, product code JIS, is a Class II 510(k) Exempt device and therefore, is not included with this submission.

PreciControl Universal, product code JJY, is a Class I 510(k) Exempt device and therefore, is not included with this submission.

9. CONCLUSIONS

The information provided in this 510(k) Premarket Notification supports the determination that the Elecsys FT4 IV assay is substantially equivalent to the predicate device, Elecsys FT4 II (K131244).