DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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July 6, 2016

ROCHE DIAGNOSTICS
EDIE EADS
REGULATORY AFFAIRS MANAGER
9115 HAGUE RD.
INDIANAPOLIS, IN 46250

Re: k153301
Trade/Device Name: Elecsys Digoxin Immunoassay
Elecsys PreciControl Cardiac II
Regulation Number: 21 CFR 862.3320
Regulation Name: Digoxin Test System
Regulatory Class: Class II
Product Code: KXT, JJY
Dated: March 9, 2016
Received: March 10, 2016

Dear Ms. Eads,

This letter corrects our substantially equivalent letter of April 8th, 2016

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. 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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K153301

Device Name
Elecsys Digoxin Immunoassay

Indications for Use *(Describe)*
Immunoassay for the in vitro quantitative determination of digoxin in human serum and plasma. Measurements are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure proper therapy. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and 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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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K153301

Device Name
PreciControl Cardiac II

Indications for Use *(Describe)*
PreciControl Cardiac II is used for quality control of specified immunoassays on the Elecsys and 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)

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Elecsys Digoxin Immunoassay
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 Elecsys Digoxin Immunoassay is an in vitro device for the quantitative determination of digoxin in human serum and plasma. Measurements are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure proper therapy.

The purpose of this Traditional 510(k) Premarket Notification is to introduce Elecsys PreciControl Cardiac II (k092649) as the control for Elecsys Digoxin Immunoassay. Additionally, Roche is modernizing the label for the Elecsys Digoxin assay, which currently does not contain information on LoB, LoD, or LoQ.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0415
Contact	Edie Eads Phone: (317) 521-4668 FAX: (317) 521-2324 Email: edie.eads@roche.com
Date Prepared	November 12, 2015
Proprietary Name	• Elecsys Digoxin Immunoassay • Elecsys PreciControl Cardiac II
Common Name	• Digoxin • PreciControl Cardiac II
Classification Name	• Enzyme Immunoassay, Digoxin • Multi-Analyte Control, All Kinds (Assayed)
Product Codes	• KXT, 862.3320 • JJY, 862.1660
Predicate Devices	Elecsys Digoxin Immunoassay (k973112)
Establishment Registration	For the Elecsys Digoxin Immunoassay, 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.

1. DEVICE DESCRIPTION

The Elecsys Digoxin assay employs a competitive test principle using a monoclonal antibody specifically directed against digoxin. Digoxin in the sample competes with the added digoxin derivative labeled with biotin for the binding sites on the ruthenylated antibody-complex.

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.

1.1. Reagents

The reagent working solutions include:

- RackPack (kit placed on instrument)
    - M: Streptavidin-coated microparticles,
    - R1: $\mathrm{Anti-digoxin-Ab{\sim}Ru(bpy)}_3^{2+}$ and
    - R2: Digoxin-derivative~biotin

1.2. Control

PreciControl Cardiac II is a lyophilized control serum based on human serum in two concentration ranges. The controls are used for monitoring the accuracy and precision of the Elecsys CK MB, CK MB STAT, Myoglobin, Myoglobin STAT, proBNP II, proBNP II STAT, and Digoxin immunoassays.

PreciControl Cardiac II includes:

- PC CARDII1: 2 bottles, each for 2.0 mL of control serum
- PC CARDII2: 2 bottles, each for 2.0 mL of control serum

2. INDICATIONS FOR USE

2.1. Elecsys Digoxin Immunoassay

Immunoassay for the in vitro quantitative determination of digoxin in human serum and plasma. Measurements are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure proper therapy.

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

2.2. Elecsys PreciControl Cardiac II

PreciControl Cardiac II is used for quality control of specified immunoassays on the Elecsys and **cobas e** immunoassay analyzers.

3. TECHNOLOGICAL CHARACTERISTICS

The following tables compare the Elecsys Digoxin assay with its predicate device, Elecsys Digoxin assay (k973112).

Table 1 Assay Comparison, General Assay Features

Feature	Predicate Device Elecsys Digoxin Immunoassay (k973112)	Candidate Device Elecsys Digoxin Immunoassay
Intended Use/Indications for Use	Immunoassay for the in vitro quantitative determination of digoxin in human serum and plasma. Measurements are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure proper therapy. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.	SAME
Assay Protocol	The Elecsys Digoxin assay employs a competitive test principle using a monoclonal antibody specifically directed against digoxin. Digoxin in the sample competes with the added digoxin derivative labeled with biotin for the binding sites on the ruthenylated antibody-complex.	SAME
Detection Protocol	Electrochemiluminescent Assay	SAME
Applications	18 minute application	SAME
Sample Type	Serum, Li-, Na-, NH+4 -heparin, K_3-EDTA, sodium citrate, and sodium fluoride/potassium oxalate plasma.	Serum, Li-Heparin, K_2- and K_3-EDTA plasma. Li-Heparin plasma tubes containing separating gel
Reagent	By incubating the sample with a digoxin specific ruthenium-labeled antibody, an immunocomplex is formed, the amount of which is dependent upon the analyte concentration in the sample. During a 2nd incubation: After addition of streptavidin-coated microparticles and a digoxin derivative labeled with biotin, the still-vacant sites of the ruthenium labeled antibodies become occupied, with formation of an antibody-hapten complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.	SAME
Calibrator	Elecsys Digoxin CalSet	SAME

Feature	Predicate Device Elecsys Digoxin Immunoassay (k973112)	Candidate Device Elecsys Digoxin Immunoassay
Calibration Interval	Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows: after 1 month (28 days) when using the same reagent lot after 7 days (when using the same reagent kit on the analyzer) as required: e.g. quality control findings outside the specified limits	SAME
Controls	A suitable commercially available control	Elecsys PreciControl Cardiac II or other suitable control material
Traceability/Standardization	This method has been standardized by weighing United States Pharmacopoeia (USP) digoxin reference material into analyte free human serum.	SAME
Reagent Stability	Store at 2-8 °C. Do not freeze. Store the Elecsys reagent kit upright in order to ensure complete availability of the microparticles during automatic mixing prior to use. Stability: unopened at 2-8 °C: up to the stated expiration date after opening at 2-8 °C: 12 weeks on the analyzers: 8 weeks	SAME

Table 2: Assay Comparison, Labeled Performance Characteristics

Feature	Predicate Device	Candidate Device
Measuring Range	0.150 (LDL)-5.00 ng/mL	0.4 ng/mL (LoQ) – 5.00 ng/mL
Precision	**Elecsys 2010 and cobas e 411** *Repeatability* HS1: 5.22% CV @ 0.85 ng/mL *Intermediate Precision* HS1: 7.69% CV @ 0.85 ng/mL	**cobas e 411** *Repeatability* HS1: 3.4% CV @ 0.565 ng/mL HS2: 2.5% CV @ 1.09 ng/mL HS3: 2.1% CV @ 1.85 ng/mL HS4: 2.3% CV @ 2.38 ng/mL HS5: 2.5% CV @ 4.67 ng/mL PC CARDII1: 2.9% CV @ 1.20 ng/mL PC CARDII2: 3.7% CV @ 2.74 ng/mL *Intermediate Precision* HS1: 6.4% CV @ 0.565 ng/mL HS2: 5.8% CV @ 1.09 ng/mL HS3: 4.5% CV @ 1.85 ng/mL HS4: 3.8% CV @ 2.38 ng/mL HS5: 6.4% CV @ 4.67 ng/mL PC CARDII1: 4.3% CV @ 1.20 ng/mL PC CARDII2: 4.1% CV @ 2.74 ng/mL
LoB	Not Reported	0.15 ng/mL
LoD	Not Reported	0.2 ng/mL
LoQ	Not Reported	0.4 ng/mL
Lower Detection Limit	0.150 ng/mL	Not Reported
Hook Effect	NA	SAME
Method Comparison	N = 81 *Passing/Bablok* y = 1.06x – 0.06 t = 0.999 *Linear regression* y = 1.09x – 0.08 r = 1.000 The sample concentrations were between approximately 0 and 3.2 ng/mL.	N = 168 *Passing/Bablok* y = 1.03x + 0.001 ng/mL t = 0.960 *Linear regression* y = 1.04x - 0.009 ng/mL r = 0.998 The sample concentrations were between approximately 0.413 and 4.78 ng/mL.

Feature	Predicate Device	Candidate Device
Limitations	1. The assay is unaffected by: Icterus (bilirubin) < 65 mg/dL, Hemolysis (Hemoglobin) < 1.0 g/dL, (Triglyceride) lipemia (Intralipid < 1500 mg/dL), Biotin < 100 ng/mL, Rheumatoid Factor <1630 IU/mL. 2. Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration. 3. No interference was observed from rheumatoid factors up to a concentration of 1630 IU/mL. 4. In vitro tests were performed on 69 commonly used pharmaceuticals. Not interference with the assay was found. 5. uzara, nabumetone, hydrocortisone, pentoxifylline and canrenone were identified to cause falsely elevated digoxin values at concentrations of the recommended daily dose. 6. Spironolactone causes elevated digoxin results above (drug) levels of 10000 ng/mL. Canrenone causes elevated digoxin results above (drug) levels of 80000 ng/mL. 7. Digoxin-like immunoreactive substances (DLIS) have been identified in blood from patients in renal failure, liver failure, and pregnant women in their third trimester. Studies have shown that the presence of DLIS in a sample can result in a false elevation of digoxin when assayed by commercially available immunoassays. 8. The manufacturer of Digoxin Immune FAb (antibody fragment therapy) has stated that no immunoassay technique is suitable for quantitating digoxin in serum from patients undergoing this treatment. 9. In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design. 10. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.	1. The assay is unaffected by: Icterus (bilirubin) < 66 mg/dL, Hemolysis (Hemoglobin) < 1.0 g/dL, (Triglyceride) lipemia (Intralipid < 1500 mg/dL), Biotin < 100 ng/mL, Rheumatoid Factor <1630 IU/mL. 2. SAME 3. SAME 4. In vitro tests were performed on a panel of commonly used pharmaceuticals. While 34 of these showed no interference with the assay 5. SAME 6. Spironolactone causes elevated digoxin results above (drug) levels of 10000 ng/mL. 7. SAME 8. As stated by the manufacturers of digitalis antidotes, the therapeutic antibody fragments against digitalis (e.g. DigiFab®, DigiBind®) will interfere with digitalis immunoassay measurements19. Therefore, the manufacturer of DigiFab® recommends to obtain samples for determination of digoxin concentration prior to antidote administration19. As a consequence Elecsys Digoxin concentrations maybe falsely elevated if measured in the presence of the antidote until the Fab fragments are eliminated from the body 9. SAME 10. SAME

4. NON-CLINICAL PERFORMANCE EVALUATION

The Elecsys Digoxin Immunoassay was evaluated for performance characteristics which are summarized below. The Elecsys PreciControl Cardiac II was evaluated for value assignment and stability studies.

4.1. Precision

Repeatability and intermediate precision of the Elecsys Digoxin assay were evaluated on one **cobas e** 411 analyzer according to CLSI EP5-A3 guideline. One reagent lot was evaluated.

A seven member panel consisting of five pooled human serum samples (HS) spiked with digoxin and two controls (PCC II = PreciControl Cardiac II, Level 1 and 2) were measured. The protocol consisted of testing 2 replicates of each control and human sera per run, divided into 2 runs per day for 21 operating days. The samples were run in randomized order on the **cobas e** 411 analyzer.

4.2. Reproducibility

Reproducibility of the Elecsys Digoxin assay was evaluated on three **cobas e** 411 analyzers according to the 3 x 5 x 5 design described in the CLSI EP5-A3 guideline. Three reagent lots were evaluated. The protocol consisted of testing 5 aliquots of each control (PCC II = PreciControl Cardiac II) and five serum sample pools spiked with digoxin.

4.3. Limit of Blank (LoB)

LoB of the Elecsys Digoxin assay was determined according to CLSI EP17-A2. For the analytical sensitivity studies, 2 **cobas e** 411 analyzers and 3 lots of reagents were used. The Limit of Blank (LoB) was determined using native human serum pools and Universal Diluent. A total of n = 60 LoB measurements were made (5 blank samples, 1 replicate, 2 runs per day on 2 instruments over 3 days).

4.4. Limit of Detection (LoD)

LoD of the Elecsys Digoxin assay was determined according to CLSI EP17-A2. For the analytical sensitivity studies, 2 **cobas e** 411 analyzer and 3 lots of reagents were used. The Limit of Detection (LoD) was determined using 5 low-level human serum samples (diluted). A total of n = 60 LoD measurements were made (5 samples, 2 runs per day on 2 instruments over 3 days).

4.5. Limit of Quantitation (LoQ)

The LoQ of the Elecsys Digoxin assay was determined according to CLSI Guideline EP17-A2. The Limit of Quantitation (LoQ) was determined using a set of ten human serum samples, three reagent lots on one **cobas e** 411 analyzer. Each sample was analyzed in replicates of 2, two runs per day over 3 days.

4.6. Linearity

Linearity of the Elecsys Digoxin assay was assessed on the **cobas e** 411 analyzer according to CLSI EP6-A. A high analyte serum sample pool spiked with digoxin was diluted with a digoxin free human serum. Fifteen concentrations (thereof 13 dilutions) throughout the measuring range were prepared. Samples were measured in 3-fold determination within a single run.

The linearity data were analyzed with regards to linear, quadratic and cubic polynomials according to CLSI EP6-A. In the first step, a linearity check was performed with a first order (linear) regression and then with higher order models (quadratic and cubic).

4.7. Dilution

The dilution study for Elecsys Digoxin assay was performed on two **cobas e** 411 analyzers using four human serum samples with Digoxin concentrations above the measuring range. Samples were diluted 1:2 manually and automatically by the instrument as recommended in the method sheet using Diluent Universal.

4.8. Human Anti-Mouse Antibodies (HAMA)

The effect of the presence of human anti-mouse antibodies in patient samples on the Elecsys Digoxin assay was assessed on the **cobas e** 411 analyzer.

A high HAMA serum pool was divided into two aliquots. The aliquots were spiked with analyte to yield two different digoxin concentrations: 0.843 and 2.37 ng/mL. Additionally, another serum pool without HAMA was divided into two aliquots and spiked with analyte to yield the same two digoxin concentrations: 0.843 and 2.37 ng/mL.

Each high HAMA serum pool was diluted in 11 steps with the corresponding non HAMA serum pool containing the same digoxin concentration. Each dilution was analyzed in 3-fold determination. Thus the digoxin concentration will remain constant, while the HAMA concentration will vary over the dilution steps. This allows for the effect of increasing amounts of HAMA on different levels of digoxin to be determined.

4.9. Endogenous Interferences

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys Digoxin assay was determined on the **cobas e** 411 analyzer using human serum samples spiked with digoxin. For each interfering substance 3 serum samples containing low, mid and high concentrations of digoxin were tested.

4.10. Exogenous Interference – Drugs

Sixteen pharmaceutical compounds were spiked into two human serum samples and tested with the Elecsys Digoxin assay on the **cobas e** 411 analyzer. The analyte concentrations of the samples were approximately 0.6 and 2.4 ng/mL. In addition, 17 special cardiac drug compounds were assessed using the same serum sample pools and tested with the Elecsys Digoxin assay on the **cobas e** 411 analyzer.

The drug concentrations were determined using available recommendations in the CLSI guideline, EP7-A2. If there was not a recommendation for concentration provided in CLSI EP7-A2, then concentrations of at least 3-times the maximum recommended daily dose were tested.

The two serum sample pools were divided into aliquots and spiked with the potential interferents. The reference sample without interferent was spiked with the respective amount of solvent only. The digoxin concentration of the spiked aliquots was determined in 3-fold determination and compared to the digoxin concentration determined for the reference aliquot (also in 3-fold determination) on a **cobas e** 411 analyzer.

4.11. Exogenous Interferences – Anticoagulants

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys Digoxin assay was determined by comparing values obtained from native samples spiked with digoxin (single donors) drawn into Serum, Li-Heparin, K2-EDTA-, and K3-EDTA-plasma primary tubes, and Li-Heparin Plasma Separation Tubes. Either 65 or 66 serum/plasma pairs per sample material were tested in duplicate with one reagent lot on a **cobas e** 411 analyzer. Potential effects were assessed by Passing/Bablok regression analysis.

4.12. Analytical Specificity/Cross Reactivity

The specificity of the Elecsys Digoxin assay was determined using two human serum samples spiked with potential cross-reactant compounds. The analyte concentration of the samples was at approximately 0.5 and 2.0 ng/mL. The spiked and non-spiked samples were tested in duplicate on the **cobas e** 411 analyzer. The difference from the non-spiked sample represents the analyte concentration simulated by cross reaction.

4.13. Method Comparison

A total of 168 human serum samples (all single donors, native as well as spiked) were measured in singleton covering the entire measuring range. Digoxin values ranged from 0.436 to 4.98 ng/mL. The study was performed on the **cobas e** 411 analyzer over 3 runs using the predicate device Elecsys Digoxin assay (k973112) (X) and the new device Elecsys Digoxin assay (Y).

4.14. Reagent Stability

To test reagent stability, four studies were executed with three studies completed.

4.14.1. Study 1: Reagent Stability After First Opening

Reagent stability after first opening for the Elecsys Digoxin assay was tested on one **cobas e** 411 analyzer. A fresh reagent rackpack was placed on the analyzer and calibrated. Reference values for the samples tested were determined. After measurement, the kit was removed from the analyzer and kept at 2-8 °C for 36, 64 and 92 days. After 36, 64 and 92 days the kit was placed on the analyzer again, calibrated, and the test samples were determined. Samples tested in duplicate include five human serum samples and two controls.

4.14.2. Study 2: On-board Reagent Stability

Refrigerated/on-board reagent stability for the Elecsys Digoxin assay was tested on the **cobas e** 411 analyzer. A fresh Reagent Rack-Pack was placed on the analyzer and calibrated. All samples were measured on Day 1. On Day 29, 57 and 64, the same samples were measured with the same reagent kit (kept at 20°C ± 3°C on-board condition) using the calibration curves established 7 days prior. Samples tested in duplicate include four human serum samples and two controls.

4.14.3. Study 3: Real-Time (Shelf-Life) Stability (ongoing)

In the real-time stability study, the Elecsys Digoxin assay material was stored at 2-8°C. The stored assay reagents were tested at time point T=0 (after manufacturing) and at specified intervals over the shelf life of the device up to the planned shelf life plus at least one month. Testing was performed using seven human serum samples covering the measuring range.

For the Master and P2 Lots, data for time points 0, 7, 10, 13, and 18 months were tested in triplicate. For the P3 Lot, data for time points 0, 3, 7, 10 and 13 months were tested in triplicate.

The recovery value was calculated as percent recovery / absolute deviation [ng/mL] of the median value compared to the reference value (Median value of two triplicate runs at T = 0).

4.14.4. Study 4: Accelerated Stability

In the accelerated stability study, the Elecsys Digoxin assay material was stored at 35°C. The stored assay reagents were tested at time point T=0 and after 3 weeks and compared to reagent stored at 2-8°C. Samples tested in duplicate include five human serum samples and two controls.

4.15. Calibration Stability

To test calibration stability, two studies were completed.

4.15.1. Study 1: Lot Calibration Stability

Calibration of an Elecsys Digoxin reagent lot is recommended every 28 days (1 month). During that time period, fresh reagent kits of the same lot can be used without calibration using the calibration curve of the Day 0 reagent kit. Elecsys Digoxin was calibrated with a fresh reagent kit on Day 1 using a **cobas e** 411 analyzer.

After 36 days, a new reagent kit of the same lot was used and recovery of samples was determined using the calibration curve of Day 1. Four human serum (HS) samples and two control samples were tested; each sample was tested with two-fold determination.

4.15.2. On-board Stability

Elecsys Digoxin reagent kits can be stored on-board the analyzers for up to 8 weeks. A new calibration of the kit kept on-board is recommended every 7 days. On-board Calibration Stability for the Elecsys Digoxin assay was tested on one **cobas e** 411 analyzer.

A fresh Reagent Rack-Pack was placed on the analyzer and calibrated. All samples were measured on Day 1. On Day 8, the same samples were measured with the same reagent kit kept at 20°C + 3°C (on-board condition) using the calibration curves established on Day 1. Samples tested include five human serum samples and two controls. Each sample was tested in two-fold determination.

4.16. Sample Stability

To test sample stability, three studies were completed.

4.16.1. Study 1: Sample Stability at 2-8°C

Seven human samples for each sample type (Serum, K2-EDTA-, K3-EDTA- and Li-Heparin-plasma) were aliquoted and measured directly (reference) and after storage at 2-8°C for 14 days. Measurements were performed with three-fold determination on a **cobas e** 601 analyzer and recovery was calculated as percent of the reference value. The samples used were all single donors spiked with digoxin.

4.16.2. Study 2: Sample Stability at Room Temperature (15-25°C)

Nine human samples for each sample type (Serum, K2-EDTA-, K3-EDTA- and Li-Heparin-plasma) were aliquoted and measured directly (reference) and after storage at 15-25°C for 7 days. Measurements were performed with three-fold determination on a **cobas e** 601 analyzer and recovery of the median was calculated as percent of the reference value. The samples used were all single donors spiked with digoxin.

4.16.3. Study 3: Sample Stability at -20°C

Eight samples for each sample type (Serum, K2-EDTA-, K3-EDTA- and Li-Heparin-plasma) were aliquoted and stored at -15 to -25°C for up to 24 months. Measurements were performed with three-fold determination on a **cobas e** 601 analyzer and median recovery was calculated as percent of the reference value (sample aliquots at -80°C). The samples used were all single donors (spiked with digoxin).

4.17. Elecsys PreciControl Cardiac II

The Elecsys PreciControl Cardiac II was evaluated for value assignment, stability, and reconstitution.

4.17.1. Value Assignment

Elecsys PreciControl Cardiac II assigned values are determined with the respective Elecsys assays. For each assay, a master calibrator set is available, which is traceable to external or internal reference material. The assigned values for Elecsys PreciControl Cardiac II are read from the master calibration curve.

Values are assigned for each lot of PreciControl Cardiac II in combination with each assay reagent lot available. The controls are run in duplicate on at least three (3) **cobas e** 601 analyzers. The assigned value of each control level is defined as the median value obtained over at least six (6) determinations (duplicate runs on at least three (3) analyzers) of the respective control level.

For additional analyzer platforms, the same value assignment procedure is performed. The assigned values obtained on the additional analyzers are compared to those obtained on the **cobas e** 601 (the master analyzer). If the difference between the median values obtained on **cobas e** 601 and **cobas e** 411 are ≤ 6% (Control Level 1 and Control Level 2), the Assigned values may be transferred from **cobas e** 601 to **cobas e** 411. Otherwise, separate assigned values are declared for each instrument platform.

4.17.2. Stability

Three studies were performed in order to verify the in-use stability claims for the Elecsys PreciControl Cardiac II (regarding Digoxin). Additionally, a real-time stability study and an accelerated stability study were performed.

4.17.2.1. Study 1: Stability at 2-8°C

The on-test and reference materials were tested in duplicate. The on-test material was reconstituted and stored for 4 days at 2-8ºC on the instrument. The reference material was a freshly reconstituted set of Elecsys PreciControl Cardiac II. The on-test recovery was calculated as a percent of the reference value.

4.17.2.2. Study 2: Open Vial After Reconstitution Stability at 20-25°C

The on-test and reference materials were tested in duplicate. The on-test material was reconstituted and stored for 4 hours at 25ºC on the instrument. The reference material was a freshly reconstituted set of Elecsys PreciControl Cardiac II. The on-test recovery was calculated as a percent of the reference value.

4.17.2.3. Study 3: Stability at -20°C after Reconstitution

The on-test and reference materials were tested in duplicate. The on-test material was reconstituted and stored for 4 months at -20°C. The reference material was a freshly reconstituted set of Elecsys PreciControl Cardiac II. The on-test recovery was calculated as a percent of the reference value.

4.17.2.4. Accelerated Stability

The on-test material was stored lyophilized at 35°C for 3 weeks. The reference material was a set of PreciControl Cardiac II stored at 2 to 8°C. After 3 weeks, the on-test and reference materials were tested in duplicate. The on-test recovery was calculated as a percent of the reference value.

4.17.2.5. Study 5: Real-Time (Shelf-life) Stability Studies

In the real-time stability study, the Elecsys PreciControl Cardiac II test material is was stored at 2-8°C. The controls were tested at specified intervals over the shelf life of the device up to the planned shelf life plus one month. The average on-test (2-8°C) recovery value was calculated as percent recovery compared to the assigned target reference value.

4.17.3. Recovery after Reconstitution

Elecsys PreciControl Cardiac II was reconstituted for 15 minutes (reference) and 30 minutes. Samples were evaluated in duplicate on the **cobas e** 411 analyzer. The average recovery after 30 minutes of reconstitution was calculated as percent recovery compared to the value obtained at 15 minutes of reconstitution (the reference value).

5. ADDITIONAL INFORMATION

The Elecsys Digoxin assay will continue to use the current Elecsys Digoxin CalSet (k973112) for calibration. There have been no changes to the CalSet.

Additionally, the Elecsys Digoxin CalCheck 5 (k102044) is used in calibration verification and for use in the verification of the assay range established by the Elecsys Digoxin. There have been no changes to the Elecsys Digoxin CalCheck 5.

6. CONCLUSIONS

The information provided in this 510(k) Premarket Notification will support a determination of substantial equivalence for the Elecsys Digoxin Immunoassay with the addition of Elecsys PreciControl Cardiac II as control.