Elecsys Syphilis
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 Elecsys Syphilis.

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Proprietary Name	Elecsys Syphilis PreciControl Syphilis PreciControl Release Syphilis
Common Name	Treponema pallidum serological reagents
Classification Name	Test, Donor, Syphilis
Product Codes, Regulation Numbers	MYR, 21 CFR 866.3830
Predicate Devices	Beckman Coulter PK TP System
Establishment Registration	Roche Diagnostics GmbH Mannheim, Germany: 9610126 Roche Diagnostics GmbH Penzberg, Germany: 9610529 Roche Diagnostics Indianapolis, IN United States: 1823260.

1. DEVICE DESCRIPTION

Elecsys Syphilis is a double antigen sandwich immunoassay with streptavidin microparticles, biotinylated recombinant TP-specific antigen labeled with a ruthenium complex and electrochemiluminescence detection. The results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration. Results greater than or equal to 1.0 COI are considered reactive for Treponema pallidum antibody. The test system contains the calibrators intended for use with the system.

1.1. Elecsys Syphilis

The reagent working solutions (the **cobas e** pack) include:

Reagent **cobas e** pack (kit placed on the analytical unit)

- M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
  Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 TP-specific recombinant antigens (E. coli)~biotin, 1 bottle, 19.7 mL:
  Biotinylated TP-specific recombinant antigens (E. coli) 0.7 mg/L,
  MES[b]) buffer 50 mmol/L, pH 6.5; preservative.
- R2 TP-specific recombinant (E. coli)~Ru(bpy) $^{2+}_{3}$, 1 bottle, 19.7 mL:
  TP-specific recombinant antigens (E. coli) labeled with ruthenium complex 0.7 mg/L, MES buffer 50 mmol/L, pH 6.5; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

Calibrators (packed with the reagent **cobas e** pack)

- SYPHB Cal1
  Non-reactive calibrator 1 (lyophilized), 2 vials each of 1.0 mL:
  Human serum, non-reactive for anti-TP antibodies; preservative.

- SYPHB Cal2
  Reactive calibrator 2 (lyophilized), 2 vials each of 1.0 mL:
  Human serum, reactive for anti-TP antibodies; preservative.

1.2. PreciControl Syphilis

The PreciControl Syphilis is a lyophilized control serum based on human serum, containing one control level reactive for anti-*Treponema pallidum* antibodies, and one control level non-reactive for anti-*Treponema pallidum* antibodies.

1.3. PreciControl Release Syphilis

The PreciControl Release Syphilis is a lyophilized control serum based on human serum, reactive for anti-*Treponema pallidum* antibodies. The control is used to validate the **cobas pro** serology solution and to release sample results for the Elecsys Syphilis immunoassay.

2. INDICATIONS FOR USE

2.1. Elecsys Syphilis

Elecsys Syphilis is an in vitro immunoassay for the qualitative detection of total antibodies (IgG and IgM) to *Treponema pallidum* in human serum and plasma. Elecsys Syphilis is intended to screen individual human donors, including volunteer donors of whole blood and blood components. This test is also intended to be used to screen organ, tissue and cell donors, when donor samples are obtained while the donor's heart is still beating. It is not intended for use on cord blood specimens.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use with the **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.

2.2. PreciControl Syphilis

PreciControl Syphilis is used for quality control of the Elecsys Syphilis immunoassay on **cobas pro** serology solution.

2.3. PreciControl Release Syphilis

PreciControl Release Syphilis is used to validate the **cobas pro** serology solution and to release the sample results for the Elecsys Syphilis immunoassay. The recovery of the release control with Roche specified limits ensures the specified sensitivity of the assay under customer site conditions.

The release control is tested at user-defined intervals with a maximum span of every 300 samples or 350 determinations and must be tested in order to release the test results. For release control values that fall outside the defined limits, samples measured before a failed release control are flagged as invalid by the **cobas pro** serology controller and need to be repeated. Reactive results will not be invalidated by a failed release control and must be retested in duplicate.

3. TECHNOLOGICAL CHARACTERISTICS

Table 1: Technical Characteristics Comparison Table between Elecsys Syphilis and Beckman Coulter PK TP System

Feature	Candidate Device Elecsys Syphilis	Predicate Device Beckman Coulter PK TP on the PK7300 System (BK060062)	Predicate Device Newmarket TP HA REAGENT on the PK7400 System (BK180301)
Intended Use	Elecsys Syphilis is an in vitro immunoassay for the qualitative detection of total antibodies (IgG and IgM) to Treponema pallidum in human serum and plasma. Elecsys Syphilis is intended to screen individual human donors, including volunteer donors of whole blood and blood components. This test is also intended to be used to screen organ, tissue and cell donors, when donor samples are obtained while the donor's heart is still beating. It is not intended for use on cord blood specimens. The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use with the **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.	Qualitative screening of blood and plasma donors for the detection of *Treponema pallidum* IgG and IgM antibodies to syphilis in human serum or EDTA plasma using the Beckman Coulter PK7200 and/or PK7300 Automated Microplate Systems.	PK7400 TP HA REAGENT is intended for the qualitative screening of blood and plasma donors for the detection of Treponema pallidum IgG and IgM antibodies to syphilis in human serum, EDTA plasma or CPDA plasma using the Beckman Coulter PK7400 Automated Microplate System. This assay is not intended for diagnostic use.
Assay Method	Double antigen sandwich assay	Hemagglutination	Hemagglutination
Detection Method	**e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA"	Photometric	Photometric
Applications/Test Time	18 minutes	60 minutes	60 minutes
Instrument Platform	**cobas pro** serology solution	PK7300	PK7400
Sample Type	Human serum, plasma	Human serum, plasma	Human serum, plasma
Sample Anticoagulants	Li-heparin, K_2-EDTA, K_3-EDTA, CPD and Na-citrate	EDTA	EDTA, CPDA
Controls	PreciControl Syphilis PreciControl Release Syphilis	PK TP System Control Set	PK7400 TP HA Controls

Feature	Candidate Device Elecsys Syphilis	Predicate Device Beckman Coulter PK TP on the PK7300 System (BK060062)	Predicate Device Newmarket TP HA REAGENT on the PK7400 System (BK180301)
Reagent Stability	Unopened at 2-8 ºC = up to the stated expiration date On the **cobas e** 801 analytical unit = 16 weeks	Unopened at 2-8 ºC = up to the stated expiration date	18 months when stored unopened at 2-8 ºC

4. NON-CLINICAL PERFORMANCE EVALUATION

The following performance data are provided in support of the substantial equivalence determination:

- Analytical sensitivity
- Sample handling and preparation
- Analytical specificity
- Cross-Reactivity
- Stability

All performance specifications were met.

4.1. Analytical Sensitivity – Limit of Blank (LoB) and Limit of Detection (LoD)

The Limit of Blank (LoB) and Limit of Detection (LoD) were determined in accordance with CLSI EP17-A2.

The limit of blank (LoB): LoB for the Elecsys Syphilis assay was estimated using five analyte-free serum and five analyte-free plasma samples measured with one reagent kit lot in duplicate determination over three days and six runs on one **cobas e** 801 analytical unit. Sixty measured values of analyte-free samples were obtained. The LoB for serum was determined to be 0.115 COI and the LoB for plasma was determined to be 0.0883 COI. Results for LoB for serum and plasma met the acceptance criteria.

The limit of detection (LoD): LoD for the Elecsys Syphilis assay was estimated using five serum and five plasma samples with low-analyte concentration (approximately four times the LoB) measured with one lot of Elecsys Syphilis in duplicate determination over three days in six runs on one **cobas e** 801 analytical unit. Sixty measured values of samples with low analyte concentration were obtained. The LoD for serum was determined to be 0.128 COI and the LoD for plasma was determined to be 0.107 COI. Results for LoD for serum and plasma met the acceptance criteria.

4.2. Sample handling and preparation

Only the following specimens listed were tested and found acceptable.

Serum and Li-heparin, K_2-EDTA, K_3-EDTA, CPD and Na-citrate plasma collected using standard sampling tubes. Serum and Li-Heparin, K_2-EDTA plasma collected in tubes containing separating gel.

Stable on-the-clot for 7 days at 15-30°C, 14 days at 2-8°C. Do not freeze samples on-the-clot.

Samples off-the-clot are stable for 7 days at 15-30°C, 14 days at 2-8°C and 12 months at -20°C (± 5°C). Samples off-the-clot may be frozen up to 4 times.

4.3. Analytical Specificity

4.3.1. Endogenous Interferences

The effect of the following endogenous substances on assay performance was tested with the Elecsys Syphilis assay on the **cobas e** 801 analytical unit. The interfering agents were tested using native or spiked serum samples. For each interfering substance five sample replicates of three human serum samples (anti-Treponema non-reactive, reactive, and high reactive) were tested with one reagent kit lot. The mean recovery (absolute deviation or percent recovery) was calculated for each sample compared to the expected (reference) value.

Interferences were tested up to the listed concentrations and no impact on results was observed.

Compound	Concentration tested
Bilirubin	≤ 753 µmol/L or ≤ 44 mg/dL
Hemoglobin	≤ 0.311 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Albumin	≤ 7.0 g/dL

Additionally, fifty samples with naturally elevated levels of triglycerides (lipemia), bilirubin, hemoglobin (hemolyzed), albumin and rheumatoid factor, respectively, were tested with the Elecsys Syphilis assay on the **cobas e** 801 analytical unit. For each interfering substance 10 human serum samples with naturally elevated levels of the interferent were tested in single determinations with one reagent kit lot; no false reactive results were found.

4.3.2. Drug Interference

Seventeen common therapeutic drugs were tested for potential interference. Each drug was tested spiked into one non-reactive sample and one anti-treponemal reactive sample. Samples were tested five-fold determination and compared to unspiked serum (reference).

Each drug was found to be non-interfering at the claimed concentrations.

Compound	Tested Concentration (mg/L)
Acetylcystein	150
Acetylsalicylic Acid	30
Ampicillin-Na	75
Ascorbic acid	52.5
Cefoxitin	750
Doxycycline	18
Heparin	3300 IU/L
Levodopa	7.5
Methyldopa	22.5
Metronidazole	123
Rifampicin	48
Acetaminophen	156
Cyclosporine	1.8
Ibuprofen	219
Theophylline	60
Phenylbutazone	321
Itraconazole	30

4.3.3. High Dose Hook Effect

A study was conducted to evaluate whether high dose hook effect can result in false non-reactive results using Elecsys Syphilis. Three high titer reactive samples were diluted in non-reactive serum in 12 dilution steps to generate a dilution series that covers the range from low-reactive to high reactive cut-off values. The diluted samples were measured on one **cobas e** 801 analytical unit in three-fold determination with one lot of Elecsys Syphilis. No false non-reactive result due to high dose hook effect was found with the Elecsys Syphilis assay.

4.4. Cross-Reactivity

A total of 170 samples containing potentially interfering factors were tested with the Elecsys Syphilis on the **cobas e** 801 analytical unit comprising specimens:

- containing antibodies against HAV, HBV, HCV, HIV, HTLV-I/II, CMV, EBV, HSV-1/2, Rubella
- containing Antinuclear Antibodies (ANA) and elevated titers of rheumatoid factor
- containing antibodies against *Escherichia coli, Toxoplasma gondii* and *Borelia burgdorferi*
- After vaccination against influenza
- From pregnant women and Multiparous Pregnancies

Results showed no interference from the above agents.

4.5. Stability

Kit stability (unopened): Kit stability/shelf-life was determined using three production lots of the Elecsys Syphilis **cobas e** pack stored refrigerated at 2-8°C, using 5 samples (non-reactive and reactive samples) and the PreciControls (PC SYPH1 B and PC SYPH2 B) in duplicate on the **cobas e** 801 analytical unit. The stability data supports Roche Diagnostic's claims as reported in the package labeling.

On-board (In-use) stability: An on-board stability study was performed for the Elecsys Syphilis **cobas e** pack to determine the time the reagent kit can be kept on-board the **cobas e** 801 analytical unit once opened. The study was performed with two non-reactive specimens, three Treponema antibody reactive specimens (COI ranged from 1 to 14.9) and the PreciControls (PC SYPH1 B and PC SYPH2 B). Samples were tested in duplicate after storage on-board for the specified time. Percent recovery for each sample was calculated compared to the unstressed Elecsys Syphilis **cobas e** pack. The stability data supports Roche Diagnostic's claims as reported in the package labeling.

PreciControl Stability (Shelf-life): Kit stability/shelf-life was determined using three production lots of the PreciControl Syphilis stored refrigerated at 2-8°C. PreciControls (PC SYPH1 B and PC SYPH2 B) were tested in triplicate on the **cobas e** 801 analytical unit. The stability data supports Roche Diagnostic's claims as reported in the package labeling.

PreciControl On-board (In-use) Stability: On-board (In-use) stability was determined using one production lot of the PreciControl Syphilis. PreciControls (PC SYPH1 B and PC SYPH2 B) were reconstituted and tested in duplicate on the **cobas e** 801 analytical unit. Reconstituted controls were stored at 20-25 °C and retested in duplicate at several time points. The stability data supports Roche Diagnostic's claims as reported in the package labeling.

4.6. Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). Precision of the Elecsys Syphilis assay demonstrated minor variability from run to run, day to day and between reagent lots. The following results were obtained:

Sample	Mean (COI)	Repeatability SD (COI)	Repeatability % CV	Between run SD (COI)	Between run % CV
HSP 01 c)	0.125	0.002	1.5	0 000	0.4
HSP 02	0 888	0.018	2.0	0 016	1.8
HSP 03	1 09	0.017	1.6	0 011	1.0
HSP 04	4.11	0.098	2.4	0 079	1.9

Sample	Mean (COI)	Repeatability SD (COI)	Repeatability % CV	Between run SD (COI)	Between run % CV
HSP 05	6 88	0.198	2.9	0 073	1.1
HSP 06	15.8	0.395	2.5	0 216	1.4
HSP 07	16.4	0.395	2.4	0.158	1.0
PC SYPH1 B d)	0.0951	0.001	1.1	0 000	0.0
PC SYPH2 B	5 90	0.126	2.1	0 087	1.5

c) HSP = human specimens

d) PC = PreciControl

Sample	Mean (COI)	Between day SD (COI)	Between day % CV	Intermediate precision SD (COI)	Intermediate precision % CV
HSP 01 c)	0.125	0.001	0.6	0 002	1.7
HSP 02	0 888	0.012	1.3	0 026	3.0
HSP 03	1 09	0.016	1.5	0 026	2.4
HSP 04	4.11	0.000	0.0	0.126	3.1
HSP 05	6 88	0.133	1.9	0 249	3.6
HSP 06	15.8	0.357	2.3	0 574	3.6
HSP 07	16.4	0.332	2.0	0 540	3.3
PC SYPH1 B d)	0.0951	0.001	0.8	0 001	1.4
PC SYPH2 B	5 90	0.025	0.4	0.155	2.6

5. EXTERNAL (CLINICAL) TESTING

5.1. Reproducibility

A study was performed based on guidance from CLSI EP05-A3 (n = 270). Testing was conducted at 3 external sites using 3 lots of the Elecsys Syphilis assay and 1 lot of PreciControl Syphilis on the **cobas pro** serology solution. Panel members and controls were tested in 2 runs per day for 5 days with 3 sample replicates per run. The reproducibility of the Elecsys Syphilis assay demonstrated minor variability from run to run, day to day and between reagent lots. The results for the Elecsys Syphilis assay are presented in the following tables.

Sample	Mean (COI)	Repeatability SD (COI)	Repeatability % CV	Between run SD (COI)	Between run % CV
HSP 01 a)	1.63	0.030	1.84	0.012	0.715
HSP 02	10.7	0.186	1.74	0.098	0.916
PC SYPH1 B b)	0.085	0.001	1.19	0.000	0.000
PC SYPH2 B	5.05	0.074	1.47	0.048	0.959

a) HSP = human specimen

b) PC = PreciControl

Sample	Mean (COI)	Between day SD (COI)	Between day % CV	Intermediate precision SD (COI)	Intermediate precision % CV
HSP 01	1.63	0.021	1.31	0.039	2.37
HSP 02	10.7	0.107	0.999	0.235	2.21
PC SYPH1 B	0.085	0.001	0.814	0.001	1.44
PC SYPH2 B	5.05	0.054	1.07	0.104	2.05

Sample	Mean (COI)	Between site SD (COI)	Between site % CV	Between lot SD (COI)	Between lot % CV
HSP 01	1.63	0.006	0.374	0.031	1.90
HSP 02	10.7	0.046	0.432	0.097	0.911
PC SYPH1 B	0.085	0.001	1.03	0.001	1.75

Sample	Mean (COI)	Between site SD (COI)	Between site % CV	Between lot SD (COI)	Between lot % CV
PC SYPH2 B	5.05	0.017	0.345	0.125	2.47

Sample	Mean (COI)	Reproducibility SD (COI)	Reproducibility % CV
HSP 01	1.63	0.050	3.06
HSP 02	10.7	0.259	2.43
PC SYPH1 B	0.085	0.002	2.49
PC SYPH2 B	5.05	0.163	3.23

5.2. Clinical Specificity

A total of 4556 specimens (2052 serum and 2504 plasma specimens) were tested at three sites with the Elecsys Syphilis assay on the **cobas pro** serology solution and FDA-cleared screening assays, including the FDA-cleared confirmatory assays. Out of the 4556 specimens, 4548 specimens were interpreted with an initial status of negative. The results of the algorithm and supplemental testing indicated that four specimens were repeatedly reactive with a negative status, and four specimens were repeatedly reactive with a positive status.

The overall specificity performance of the Elecsys Syphilis assay was 99.91% with a 95% CI of 99.77% to 99.97%.

The initial and repeat reactive rates were 0.10 % (2/2052) for the serum specimens and 0.24 % (6/2054) for the plasma specimens

Specimen Category	Number tested	Number IR a) (% of total)	Number RR b) (% of total)	Number by Supplemental Testing (% of RR)	Specificity (%) (95 % CI)
Volunteer blood donors - serum	2052	2 (0.10)	2 (0.10)	2 (100)	100 (2050/2050) (99.81, 100)
Volunteer blood	2504	6	6	2	99.84

Specimen Category	Number tested	Number IR a) (% of total)	Number RR b) (% of total)	Number by Supplemental Testing (% of RR)	Specificity (%) (95 % CI)
donors - plasma		(0.24)	(0.24)	(33.3)	(2498/2502) (99.59, 99.94)
Total donors	4556	8 (0.18)	8 (0.18)	4 (50.0)	99.91 (4548/4552) (99.7, 99.97)

a) IR = initially reactive

b) RR = repeatedly reactive

5.3. Clinical Sensitivity

Five hundred and fifty-two specimens (201 serum, 351 plasma) were tested for evaluating the sensitivity of the Elecsys Syphilis assay on the **cobas pro** serology solution, using three reagent kit lots distributed among three test-sites. All 552 specimens showing a positive syphilis specimen status were congruently repeatedly reactive with the Elecsys Syphilis assay. The sensitivity was calculated to be 100 % (552/552) with a 95 % confidence interval of 99.31 % to 100 %.

Combined (serum and plasma)

Specimen category	Specimen status Positive	Number RR	Sensitivity (%) (95% CI)
Latent infection	97	97	100 (96.19, 100)
Primary infection	76	76	100 (95.19, 100)
Secondary infection	64	64	100 (94.34, 100)
Uncharacterized syphilis infection	315	315	100 (98.80, 100)
Total	552	552	100 (99.31, 100)

Serum

Specimen category	Specimen status Positive	Number RR	Sensitivity (%) (95% CI)
Latent infection	70	70	100 (94.80, 100)
Primary infection	50	50	100 (92.87, 100)
Secondary infection	63	63	100 (94.25, 100)
Uncharacterized syphilis infection	18	18	100 (82.41, 100)
Total	201	201	100 (98.12, 100)

Plasma

Specimen category	Specimen status Positive	Number RR	Sensitivity (%) (95% CI)
Latent infection	27	27	100 (87.54, 100)
Primary infection	26	26	100 (87.13, 100)
Secondary infection	1	1	100 (20.65, 100)
Uncharacterized syphilis infection	297	297	100 (98.72, 100)
Total	351	351	100 (98.92, 100)

6. CONCLUSIONS

The results of non-clinical analytical and clinical performance studies demonstrate that the Elecsys Syphilis test for use on the **cobas pro** system when equipped with the **cobas e** 801 analytical unit is as safe, as effective, and performs as well as the predicate device.