SUMMARY OF SAFETY AND EFFECTIVENESS

Product

1. General Information

Device Generic Name:	Elecsys HIV combi PT
Device Trade Name:	Elecsys HIV combi PT PreciControl HIV Gen II PreciControl HIV; HIV-2 + Grp O
Device Product Code:	MZF
Applicant Name and Address:	Roche Diagnostics 9115 Hague Road Indianapolis, IN 46250 Phone: 317 521 7144 Fax: 317 521 2334
Establishment Registration Number:	1823260
Premarket Approval Application (PMA) Number:	BP160050
Date of Panel Recommendation:	Not Applicable
Office's Signatory Authority	Jay S Epstein, M.D. Director, OBRR/CBER

□ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Date of FDA Notice of Approval:

Material Reviewed/Consulted: The PMA, amendments to the PMA, and other specific documentation used in developing the Summary of Safety and Effectiveness (SSE)

Review memos from the following reviewers were used in developing the SSE:

Discipline	**Reviewer Names**
Product Design	Mohan Kumar Haleyur Giri Setty
Chemistry/Manufacturing/Controls (CMC)	Mohan Kumar Haleyur Giri Setty Krishnakumar Devadas Yongqing Chen Jiangqin Zhao Xue Wang
Preclinical Studies and Clinical Studies	Mohan Kumar Haleyur Giri Setty Krishnakumar Devadas Xue Wang Andrew Dayton Paul Hshieh Pawan Jain
DMPQ/pre-approval inspection	Lori Peters
Bioresearch Monitoring Inspection (BIMO)	Carla Jordan
Statistician	Paul Hshieh
Instrumentation and Software	Sajjad Syed Yongqin Chen Babita Mahajan
Product and Promotional Labeling OCBQ/DCM/APLB	Dana Martin Mohan Kumar Haleyur Giri Setty

2. Intended Use

The Elecsys HIV combi PT is an immunoassay for the in vitro qualitative detection of HIV-1 p24 antigen and antibodies to HIV-1 (HIV-1 groups M and O) and HIV-2 in human serum and plasma. The Elecsys HIV combi PT is intended to be used as an aid in the diagnosis of HIV-1 and/or HIV-2 infection, including acute or primary HIV-1 infection. The assay may also be used as an aid in the diagnosis of HIV-1/HIV-2 infection in subjects older than 2 years of age and in pregnant women.

The Elecsys HIV combi PT immunoassay is not intended for the screening of blood or plasma donors.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on the **cobas e** 602 immunoassay analyzer.

A reactive result using the Elecsys HIV combi PT immunoassay does not distinguish HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody, and HIV-1 group O antibody.

The PreciControl HIV Gen II and the PreciControl HIV; HIV-2 + Grp O are intended to be used for quality control of the Elecsys HIV combi PT immunoassay on the **cobas e** 602 immunoassay analyzer.

3. Description: Elecsys HIV combi PT

3.1 Device Description

The Elecsys HIV combi PT is a qualitative serologic sandwich immunoassay intended for the detection of HIV-1 p24 antigen and antibodies to HIV-1, including group O, and HIV-2 in human serum or plasma. This assay uses recombinant antigens derived from the envelope and polymerase region of HIV-1 and HIV-2 to determine HIV-specific antibodies and is based on the electrochemiluminescence immunoassay (ECLIA) principle.

In the first incubation step, 39 µl of the specimen is pretreated with detergent. In the second incubation step, biotinylated monoclonal anti-p24 antibodies, biotinylated HIV-specific recombinant antigens, biotinylated HIV-specific peptides and ruthenylated monoclonal anti-p24 antibodies, ruthenylated HIV-specific recombinant antigens, and ruthenylated HIV-specific peptides are added to form a sandwich complex. In the third incubation step, the sandwich complex is captured by streptavidin-coated micro particles. This reaction mixture is aspirated into the measuring cell of the analyzer where the micro particles are magnetically captured onto the surface of an electrode. Residual unbound substances are removed with ProCell M. Application of a voltage to the electrode induces electrochemiluminescent emission which is measured by a photomultiplier. The level of signal increases as the concentration of the anti-HIV antibodies and antigens present in a patient specimen increases.

The Elecsys HIV combi PT immunoassay requires the use of quality control reagents, the PreciControl HIV Gen II and the PreciControl HIV; HIV-2+ Grp O. Results are determined using instrument-specific two-point calibration curves and master curves provided via reagent barcodes.

The Elecsys HIV combi PT immunoassay employs the electrochemiluminescence "ECLIA" technology which has been reviewed and approved by FDA in prior PMA submissions; P990012/S012 for the Elecsys HBsAg Immunoassy, P000027/S012 for the Elecsys Free PSA Immunoassay and P090008/S006 for the Elecsys Anti-HCV Immunoassay. The assay is intended for use on the Roche **cobas e** 602 analyzer, which is part of the **cobas** 8000 Modular Analyzer

Series that was cleared under 510(k) number K100853.

3.2. Kit Configurations and Components

The Elecsys HIV combi PT immunoassay is available in a 100-test kit size. It consists of six reagent components supplied by Roche Diagnostics in a single package. Three of these components are combined in a bundled reagent pack, the so-called "rackpack", which is placed in the instrument, together with the Pre-Treatment reagent "R0" while operational. All reagent components of the Elecsys HIV combi PT immunoassay are labelled with barcodes.

The PreciControl HIV Gen II and PreciControl HIV; HIV-2 + Grp O are required for quality control of the Elecsys HIV combi PT immunoassay and are sold separately.

The kits consist of three reagent components (PreciControl HIV Gen II, 2 bottles each), and two reagent components (PreciControl HIV; HIV-2 + Grp O, 2 bottles each), supplied by Roche Diagnostics in a single package.

3.2.1. Reagent Components

The Elecsys HIV combi PT immunoassay kit consists of six components.

There are two reagent cassettes comprised of 4 bottles (components M, R0, R1, and R2) and two calibrator components (Cal1 and Cal2).

Table 1A. Elecsys HIV combi PT Kit Components

Name	Description
M	Streptavidin-coated microparticles
R0	Pretreatment reagent
R1	Biotinylated monoclonal anti-p24 antibodies, Biotinylated HIV-1/-2-specific recombinant antigens, Biotinylated HIV-1/-2 specific peptides
R2	Ruthenylated monoclonal anti-p24 antibodies, Ruthenylated HIV-1/-2-specific recombinant antigens, Ruthenylated HIV-1/-2 specific peptides
HIVCOMPT Cal1	Negative calibrator 1
HIVCOMPT Cal2	Positive calibrator 2

The reagents "M", "R1" and "R2" are combined in the rackpack, a bundle of three reagent bottles, which is placed on the instrument as a single unit. "R0", is placed as a separate unit on the analyzer. All reagents which are part of the rackpack are provided ready for use. The Calibrators are provided lyophilized and need to be reconstituted before use. R0 is provided as a ready to use reagent.

3.2.2. PreciControl Components

The PreciControl HIV Gen II and the PreciControl HIV; HIV-2 + Grp O are used for quality control of the Elecsys HIV combi PT immunoassay on the **cobas** e 602 immunoassay analyzer.

The control kit consists of two separate packages containing five lyophilized reagents in total, with PreciControl HIV1-3 in one package that is labelled as the PreciControl HIV Gen II, and PreciControl HIV4 and 5 in another separate package that is labelled as PreciControl HIV; HIV- 2 + Grp O:

- PreciControl HIV1 contains human serum, negative for HIV (antigen and antibody)
- PreciControl HIV2 contains inactivated positive human serum for anti-HIV-1 antibodies
- PreciControl HIV3 contains HIV-1 p24 antigen in human serum
- PreciControl HIV4 contains inactivated positive human serum for anti-HIV-2 antibodies
- PreciControl HIV5 contains anti-HIV-1 subtype Grp O monoclonal mouse antibodies in human serum

Table 1B. PreciControl HIV Gen II and PreciControl HIV; HIV-2 + Grp O Components

Control Kits	Components	Description
PreciControl HIV Gen II	PC HIV1	PreciControl HIV1, negative for HIV (antigen and antibody)
	PC HIV2	PreciControl HIV2, positive for anti-HIV-1 antibodies
	PC HIV3	PreciControl HIV3, positive for HIV-1 p24 antigen
PreciControl HIV; HIV-2 + GrpO	PC HIV4	PreciControl HIV4, positive for HIV-2 antibodies
	PC HIV5	PreciControl HIV5, positive for HIV-1 group O antibodies

3.2.3. System Reagents for cobas e 602 Analyzer

For processing any Elecsys Immunoassay on the **cobas e** 602 analyzer, specific system reagents are required, which are packaged and sold separately. The required system reagents are common for use with all marketed Elecsys and **cobas e** immunoassays.

Table 2. System Reagents Required for Elecsys Immunoassays on the cobas e 602 Analyzer

Catalog No.	Component/Reagent	Component Volume	Quantity	Type of Material
0488 0340	ProCell M	2L	2	System buffer
0488 0293	CleanCell M	2L	2	Measuring cell cleaning solution
1129 8500	Elecsys SysClean	100 mL	5	System cleaning solution
0300 5712	ProbeWash M	70 mL	12	Cleaning solution for run finalization and rinsing
0300 4899	PreClean M (for prewash assays)	600 mL	5	Detection cleaning solution

3.2.4. Materials Provided

- Working Solutions reagents.
- 2 x 6 bottle labels and 4 empty labeled snap-cap bottles

3. 2.5. Materials required (but not provided)

- PreciControl HIV Gen II; 2 x 2 mL each of PreciControl HIV Gen II 1, 2, and 3
- PreciControl HIV; HIV-2+ Grp O for 2 x 2mL each of PreciControl HIV; HIV-2+ Grp O 4 and 5
- CalSet Vials
- 2 x 56 empty snap-cap bottles
- **cobas e** 602 analyzer
- Distilled or deionized water

3.2.6. Accessories for cobas e 602 analyzer:

- ProCell M, 2 x 2 L system buffer
- CleanCell M
- 2 x 2 L measuring cell cleaning solution
- PC/CC-Cups- 12 cups to prewarm ProCell M and CleanCell M before use
- ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- PreClean M, 5 x 600 mL detection cleaning solution
- Assay Tip/AssayCup Combimagazine M
- 48 magazines x 84 reaction vessels or pipette tips
- WasteLiner, waste bags and SysClean Adapter M

4. Test Procedure

4.1. Specimen Collection, Preparation, and Storage

4.1.1. Collecting Specimens

The Elecsys HIV combi PT assay can be performed on serum and plasma specimens collected by venipuncture following the instructions provided with the specimen collection device for use and processing. Specimens are processed by centrifugation followed by physical separation of the serum from the clot. Complete clot formation should take place before centrifugation. The centrifugation step may occur up to 24 hours post draw. Specimens with obvious microbial contamination should not be used.

Specimen types listed below are acceptable for testing with Elecsys HIV Combi PT.

- Serum collected using standard sampling tubes or tubes containing separating gel.
- Li-heparin, K2-EDTA and K3-EDTA plasma as well as Li-heparin plasma tubes containing separating gel.

4.1.2. Storing Specimens

Specimens collected are stable for 4 weeks for storage and transport at 2 - 8 °C, 7 days at 25 °C, and 3 months at -20 °C. Specimens may be frozen and thawed up to 5 times. Specimen collection systems from various manufacturers may contain differing materials which could affect test results in some cases. When processing specimens in primary tubes (specimen collection systems), instructions of the tube manufacturer should be followed. Specimens containing precipitates and frozen/thawed specimens should be centrifuged before performing the assay.

4.2. Calibration

Calibration must be performed once per reagent lot using HIVCOMPT Cal1, HIVCOMPT Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

According to the product specification, one calibrator set may be used only once. Unless the entire volume is necessary for calibration on the analyzer, aliquots of the ready-for-use calibrators may be transferred into empty snap-cap bottles (CalSet vials) and should be left on the **cobas e** 602 analyzer only during calibration (5 hours in total).

4.2.1. 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 with PreciControl HIV Gen II and PreciControl HIV; HIV-2 + Grp O outside the defined limits

• More frequently when this is required by pertinent regulations

4.2.2. Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HIVCOMPT Cal1): 550 - 2200 (**cobas e** 602 analyzers)

Positive calibrator (HIVCOMPT Cal2): 14000 - 70000 (**cobas e** 602 analyzers)

4.3. Quality Control

PreciControl HIV Gen II and PreciControl HIV; HIV-2 + Grp O are used for quality control of the Elecsys combi PT assay. All controls should be run individually at least once every 24 hours when the test is performed, once per reagent kit lot, and following each calibration. The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside defined limits.

5. Interpretation of Results

Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the specimen with the signal of the cutoff value previously obtained by calibration. The result of a specimen is given either as reactive or non-reactive as well as in the form of a cutoff-index (specimen signal/ cutoff). Specimen with a cutoff index < 1.0 are non-reactive and these specimens are considered negative for HIV-1 Ag and HIV-1/-2 specific antibodies and do not need further testing. Specimens with a cutoff index ≥ 1.0 are considered reactive. The test design of the Elecsys HIV combi PT immunoassay is that of a qualitative assay format with a cutoff threshold.

The Elecsys HIV combi PT results are calculated by first subtracting the instrument background signal from the total signal.

Adjusted signal = total signal – instrument background

6. Limitations of the Test

- The Elecsys HIV combi PT assay is for in vitro diagnostic use only.
- This assay is not for screening blood or plasma donors.
- The Elecsys HIV combi PT assay is limited to the detection of p24 antigen and/or antibodies to HIV-1 (HIV-1 groups M and O) and/or HIV-2 in human serum and plasma.
- Elecsys HIV combi PT assay does not distinguish HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody, and HIV-1 group O antibody.
- Heat-inactivated specimens and specimens stabilized with azide should not be used. Specimens should be at 20 - 25 °C prior to use with the assay.
- Due to possible evaporation effects, specimens placed on the analyzers should be analyzed or measured within 2 hours.
- The calculated values for anti-HIV and/or p24 antigen in a given specimen as determined by assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with different assay

methods cannot be used interchangeably. The reported antibody level and/or p24 antigen cannot be correlated to an endpoint titer.

- Heterophilic and Human Antibodies to Mouse antigens (HAMA) in human specimens can react with reagent antibodies, interfering with in vitro immunoassays. Patients routinely exposed to animals or animal serum products for diagnosis or therapies can be prone to this interference and anomalous values may be observed. Specimens from patients who have received mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies and may interfere in assays that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.

- The performance of the Elecsys HIV combi PT assay has not been established with cord blood, neonatal specimens, cadaver specimens, heat-inactivated specimens, or body fluids other than serum and plasma such as saliva, urine, and amniotic or pleural fluids.

- The Elecsys HIV combi PT assay may not detect all infected individuals. A negative test result does not exclude the possibility of exposure to or infection with HIV. HIV antibodies and/or p24 antigen may be undetectable in some stages of the infection and in some clinical conditions.

- A person who has antigen or antibodies to HIV is presumed to be infected with the virus. However, a person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV.

- The claims, including those pertaining to sample stability made in the labeling of the cleared/approved reagents of Roche Diagnostics are part of the clearance of the overall IVD test system (assay). Sample stability was tested only for the temperatures/time frame as claimed by the manufacturer under the conditions claimed in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

7. (b) (4)

8. Marketing History

The Elecsys HIV combi PT is currently marketed globally in 53 countries. The device has not been withdrawn to date from the market in any country for reasons relating to safety and effectiveness of the device.

9. Potential Adverse Effects of the Device on Health

Potential adverse effects of the Elecsys HIV combi PT assay relate to the risk of false positive and false negative results. While performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exist. The risk of incorrect results is minimized by following the procedures and instructions outlined in the Package Insert.

10. Summary of Preclinical Studies

10.1. Determination of Cutoff

Studies were performed to establish and verify the cutoff by defining variables of the cutoff formula for the Elecsys HIV combi PT. A cutoff was established to enable a specificity of (b) (4) and to ensure that no false negative results are observed in the specimens tested.

10.2. Determination of Limit of Blank and Limit of Detection

The Limit of Blank (LoB) and Limit of Detection (LoD) for the Elecsys HIV combi PT assay were determined in accordance with (b) (4) . LoB is defined as the concentration at which there is a (b) (4) . LoD is defined as the concentration at which there is a (b) (4) .

For determination of the Limit of Blank (LoB), (b) (4) **cobas e** 602 analyzer. In total, (b) (4) measured values of (b) (4) specimens were obtained. Data analysis was based on determination of the (b) (4) values. For determination of the Limit of Detection (LoD), (b) (4) specimens with (b) (4) concentration (approximately (b) (4) the LoB) were measured in (b) (4) **cobas e** 602 analyzer. In total, (b) (4) measured values of specimens with (b) (4) concentrations were obtained. Data analysis of the (b) (4) measured values was as follows:

(b) (4)

Results: The Elecsys HIV combi PT assay LoB was determined to be (b) (4) as defined above was (b) (4) .

10.3. HIV-1 p24 Ag Analytical Sensitivity

Analytical sensitivity of the Elecsys HIV combi PT immunoassay for detection of HIV-1 p24 antigen only was evaluated using the (b) (4) HIV-1 p24 Antigen, NIBSC code (b) (4) HIV-1 antigen diluted with HIV negative serum. (b) (4) dilutions of each standard were prepared and measured. Measurements on the **cobas e** 602 analyzer were performed in (b) (4) determinations with three lots of the Elecsys HIV combi PT immunoassay. Sensitivity was calculated using the mean of three lots tested by reading off the concentration at the cutoff from the HIV-Ag reference standard curve.

Results: The analytical antigen sensitivity of the Elecsys HIV combi PT as measured by (b) (4) was shown to be (b) (4).

10.4. HIV Antigen reactivity (HIV-1 M Subtypes, HIV-1 Group O, and HIV-2)

The purpose of this study was to evaluate reactivity of the Elecsys HIV combi PT with 48 HIV antigen lysates from cell culture supernatants of HIV-1 M subtype A, B, C, D, E, F, G, H, CRF01 AE, and CRF02 AG, HIV-1 Group O, two unknown HIV-1 subtypes and HIV-2. To determine reactivity, all 48 viral antigen lysates were tested in triplicate with the Elecsys HIV combi PT.

Table 3. Detection of HIV-1 and HIV-2 Antigens in Culture Supernatants

HIV Type/ Group/Subtype	Number tested	Number reactive
A	3	3/3
B	6	6/6
C	4	4/4
D	3	3/3
E	3	3/3
F	1	1/1
G	2	2/2
H	1	1/1
HIV-1 unknown subtype	2	2/2
HIV-1 CRF01 AE	3	3/3
HIV-1 CRF02 AG	5	5/5
HIV-2	5	5/5
HIV-1 Group O	10	10/10

Table 3. Summary: All 48 viral lysates were reactive on the Elecsys HIV combi PT assay.

Results: All 48 viral lysate specimens were reactive with the Elecsys HIV combi PT as shown in the Table 3. The assay demonstrates acceptable performance for the detection of HIV-1 and HIV-2 antigens.

10.5. Detection of Worldwide HIV-1 group M subtype in clinical specimens

The HIV-1 group M cohort from outside the US was tested using the Elecsys HIV combi PT assay and an FDA approved HIV antigen/antibody assay. The HIV-1 group M cohort consisted of a total of 85 antigen positive specimens across 6 different subtypes: A, B, C, D, circulating recombinant form, CRF01_AE and circulating recombinant form, CRF02_AG. All 85 subjects had a final diagnosis of HIV positive.

Table 4. **Detection of Worldwide HIV-1 group M subtype in clinical specimens**

Subtype	Number of specimens tested	Elecsys HIV combi PT	FDA Approved assay
A	15	15/15	15/15
B	15	15/15	15/15
C	15	15/15	15/15
D	15	15/15	15/15
CRF01_AE	15	15/15	15/15
CRF02_AG	10	10/10	10/10

Table 4. Summary: All 85 specimens were positive using the Elecsys HIV combi PT assay.

Results: Sensitivity was determined to be 100. % with a 95 percent confidence interval of 95.80 to 100 %. The assay demonstrates acceptable performance.

10.6. Seroconversion Panels

Seroconversion sensitivity of the Elecsys HIV combi PT was shown by testing twenty commercially-sourced seroconversion panels with a total of 140 specimens and comparing Elecsys HIV combi PT results to the certificate of analysis based on the FDA approved assay or, if that is not available, with the current results of the FDA approved reference assay.

Table 5. Elecsys HIV combi PT Assay Reactivity in Seroconversion Panels

	FDA Approved HIV Ag/Ab combo assay		Elecsys HIV combi PT		Difference in Panel Number to the Elecsys HIV combi PT Reactivity
Panel ID	NR[a]	RX[b]	NR[a]	RX[b]	
PRB933	0	21	0	21	0
PRB942	9	14	9	14	0
PRB943	5	7	5	7	0
PRB946	4	7	4	7	0
PRB948	20	23	20	23	0
PRB951	2	8	2	8	0
PRB955	0	3	3	7	-4 (difference of 1 bleed)
PRB956	42	47	42	47	0
PRB958	2	7	2	7	0
PRB960	21	28	21	28	0

	FDA Approved HIV Ag/Ab combo assay		Elecsys HIV combi PT		Difference in Panel Number to the Elecsys HIV combi PT Reactivity
6243	20	25	25	27	-2 (difference of 1 bleed)
6244	26	28	26	28	0
6247	21	23	21	23	0
9011	28	36	28	36	0
9012	14	16	14	16	0
6248	14	18	14	18	0
9019	3	38	3	38	0
9013	23	25	23	25	0
9015	21	30	21	30	0
9016	27	30	27	30	0

[a]NR represents the last draw with a non-reactive result in days since the first draw.

[b]RX represents the first draw with a reactive result in days since the first draw

Table 5. Summary: The table compares the results of seroconversion panels tested using the FDA approved and Elecys HIV combi PT assays.

Results: Seroconversion testing resulted in positive detection with the Elecsys HIV combi PT one bleed later than with the FDA approved assay in two panels. Equivalent performance was observed in 138 of the 140 total bleeds tested.

10.7. Elecsys HIV combi PT Reactivity with Specimens Reactive for HIV-1 p24 Antigen, Antibody Negative and Western Blot Negative / Indeterminate

The sensitivity of HIV combi PT was determined in a multi-site study in a total of 27 antigen positive, antibody negative and western blot negative / indeterminate specimens. The cohort consisted of specimens from seroconversion panels and identified as authentic p24 antigen positive based on the certificate of analysis. A total of 26 specimens were initially reactive using the Elecsys HIV combi PT and the FDA approved assay.

Table 6. Elecsys HIV combi PT Reactivity with Specimens Reactive for HIV-1 p24 Antigen, Antibody Negative and Western Blot Negative/ Indeterminate

	Elecsys HIV combi PT Assay			FDA Approved HIV Assay	
Specimen Population	**Number Tested**	**Non-reactive**	**Reactive**	**Non-reactive**	**Reactive**
Authentic p24 Ag+/Ab- Specimens	27	1	26	1	26
Total	27	1	26	1	26

Table 6. Summary: The table compares results of HIV-1 p24 antigen only specimens tested using the FDA approved and Elecys HIV combi PT assays

Results: The sensitivity of the Elecsys HIV combi PT for HIV p24 antigen only specimens was 96.30% with a 95% confidence interval of 81.03% to 99.91%. Out of 27 specimens tested 26 were positive on both FDA approved assay and on the Elecsys HIV combi PT assay.

10.8. Hook Effect

The Elecsys HIV combi PT Immunoassay was evaluated for "High Index hook" effects in specimens containing extremely high HIV titers. Eight high titer positive specimens were diluted each in HIV negative serum in 11 dilution steps to generate a dilution series that cover the range from negative to high positive S/CO values and the specimens were measured in single determination.

Results: Results obtained indicated that the Elecsys HIV combi PT immunoassay did not exhibit a high-dose hook effect up to the levels tested. The results demonstrate acceptable performance.

10.9. Effect of Potentially Interfering Substances

The Elecsys HIV combi PT assay was tested for interference by high levels of endogenous substances. Several interfering agents were tested using natural or spiked serum and plasma specimens (for rheumatoid factor only plasma specimens were used). Serum specimens were taken from single donors and plasma specimens from pool matrix and single donors. Dilution series with two dilution steps (eleven dilution steps for biotin) each were prepared for serum specimens for all interfering substances by diluting specimens spiked with a high concentration of the interference substances with the corresponding unspiked specimens. Specimens were tested in duplicates. Percent mean recovery of S/CO values of specimens spiked with interfering substance were calculated against the respective specimens without the interfering substance.

Table 7. Concentration of Interfering Substances

Substance	Concentration
Hemoglobin	500mg/dL
Intralipid® (Lipemia)	1500 mg/dL
Bilirubin	60 mg/dL
Biotin in serum	63 ng/mL
Biotin in Plasma	49 ng/mL
Human Serum Albumin	10 g/dL
Rheumatoid Factor	1500 IU/mL

Results: None of the potentially interfering substances at the levels tested produced a change in the interpretation of the assay. The results demonstrate acceptable performance at the tested level listed in the above table.

10.10. Interference by Unrelated Medical Conditions:

To assess potential interference by unrelated medical conditions, specimens containing potentially interfering factors were tested using the Elecsys HIV combi PT. Specimens were tested neat and spiked separately with HIV-1 antibody positive specimens, HIV-2 antibody positive specimens or HIV-1-p24 antigen positive specimens. Spiking was performed at levels near the cutoff of the

Elecsys HIV combi PT. Measurements were performed in singlicate with one lot of the Elecsys HIV combi PT. The results are presented in Table 8, below:

Table 8. Effect of Potentially Interfering Medical Conditions on sensitivity of Elecsys HIV combi PT

Clinical Category	Number Tested	Reactivity on Elecsys HIV combi PT
CMV	9	0/9
EBV	10	0/10
HSV	10	0/10
HAV	10	0/10
Rubella	5	0/5
HBV	9	0/9
HCV	9	0/9
ANA	11	0/11
Rheumatoid Factor	33	0/33
Malaria	11	0/11
E.coli	11	0/11
Tuberculosis	10	0/10
HTLV	11	0/11
Candida	10	0/10
Influenza Pre Vaccination	8	0/8
Influenza Post Vaccination	8	0/8
HAV/HBV Pre Vaccination	14	0/14
HAV/HBV Post Vaccination	14	0/14
Pregnant 1st Trimester	30	0/30
Pregnant 2nd Trimester	30	0/30
Pregnant 3rd Trimester	30	0/30

Table 8. Summary: The Elecsys HIV combi PT assay showed no false positive results in neat specimens and no false negative results in the spiked specimens.

Results: The presence of potentially interfering substances or medical conditions had no significant effect on the detection of HIV-1 antibodies, HIV-2 antibodies, or HIV-1 antigen (data not shown) and no significant effect on background signal in negative specimens (neat specimens). The results demonstrate acceptable performance.

10.11. Drug Interference

To assess potential interference by therapeutic drugs according to CLSI EP07-A2, eighteen common therapeutic drugs were tested. Each drug was separately spiked into a negative, an anti-HIV antibody positive (S/CO 2 - 4) and an HIV-Ag positive specimen (S/CO 2 - 4) at a concentration 3-10 times the maximum daily dosage. Testing was done in triplicate, with comparison to unspiked serum tested nine-fold, by calculating the mean S/CO values, and standard deviations (SD). The concentration of drugs used for testing is shown in Table 9 below:

Table 9. Concentration of Drugs

Compound	Concentration (mg/L)
Acetyl cysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cyclosporine	5
Cefoxitin	2500
Heparin	5000 U/L
Levodopa	20
Methyldopa+ 1.5	20
Metronidazole	200
Phenylbutazone	400
Doxycycline	50
Acetylsalicylic acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophylline	100
Tetracycline	50
Ca-Dobesilate	200

Results: Each drug was found to be non-interfering at the concentrations tested.

10.12. Precision and Reproducibility studies:

A reproducibility study was conducted at three external sites on the **cobas e** 602 analyzer using three lots of reagent and one lot each of PreciControl HIV Gen II and PreciControl HIV; HIV-2+Grp O. Pools for the precision testing included eight spiked human serum pools and control pools. Precision pools and PreciControl pools were run using the experimental design consisting of 2 aliquots per specimen per part in singlet replication with 2 parts per day for 21 days.

Table 10. Summary of Precision and Reproducibility for the Elecsys HIV combi PT

Specimen type		Repeatability		Inter-Run		Inter-Day		Inter-Site*Lot		Inter-Site		Inter-Lot		Reproducibility	
	Mean	SD	CV[%]	SD	CV[%]	SD	CV[%]	SD	CV[%]	SD	CV[%]	SD	CV[%]	SD	CV[%]
HSP.06	2.03	0.087	4.30	0.018	0.88	0.045	2.22	0.022	1.08	0.024	1.18	0.058	2.87	0.120	5.91
HSP.07	51.2	2.01	3.93	0.000	0.00	0.489	0.95	0.666	1.30	0.639	1.25	1.27	2.48	2.59	5.07
HSP.08	1.43	0.049	3.46	0.000	0.00	0.022	1.56	0.020	1.37	0.011	0.77	0.058	4.07	0.083	5.78
HSP.09	38.2	1.30	3.42	0.000	0.00	0.368	0.96	0.378	0.99	0.563	1.47	0.89	2.34	1.76	4.61
HSP.10	2.25	0.157	6.97	0.000	0.00	0.029	1.29	0.033	1.46	0.027	1.19	0.066	2.94	0.177	7.90

Specimen type		Repeatability		Inter-Run		Inter-Day		Inter-Site*Lot		Inter-Site		Inter-Lot		Reproducibility	
HSP.11	58.7	1.97	3.35	0.000	0.00	0.227	0.39	0.756	1.29	0.656	1.12	2.31	3.94	3.21	5.46
HSP.12	4.39	0.181	4.13	0.000	0.00	0.000	0.00	0.046	1.05	0.067	1.52	0.216	4.93	0.294	6.69
HSP.13	0.082	0.014	17.59	0.011	12.95	0.007	8.90	0.009	10 94	0.000	0.00	0.021	25 94	0.030	36.73
PC.HIV1	0.209	0.018	8.79	0.008	3.81	0.008	4.03	0.011	5.47	0.000	0.00	0.035	16 56	0.042	20.31
PC.HIV2	4.83	0.168	3.48	0.000	0.00	0.035	0.72	0.048	0.99	0.035	0.73	0.165	3.41	0.245	5.08
PC.HIV3	3.92	0.117	2.99	0.032	0.83	0.050	1.27	0.050	1.26	0.000	0.00	0.093	2.37	0.168	4.30
PC.HIV4	5.01	0.127	2.54	0.000	0.00	0.050	1.00	0.054	1.07	0.042	0.84	0.286	5.71	0.324	6.47
PC.HIV5	5.17	0.169	3.28	0.000	0.00	0.061	1.19	0.065	1.26	0.073	1.42	0.233	4.50	0.310	6.00

Specimen type: PC HIV1- Negative for HIV (antigen and antibody), PC HIV2- Positive for anti-HIV-1 antibodies, PC HIV3- Positive for HIV p24 antigen, PC HIV4- Positive for HIV-2 antibodies, PC HIV5- Positive for HIV-1 (Group O) Antibodies, HSP 06- HIV-1 antibody group M low positive sera, HSP 07- HIV-1 antibody group M high positive sera, HSP 08- HIV Ag low positive sera, HSP 09- Ag high positive sera, HSP 10- HIV-2 Ab low positive sera, HSP 11- HIV-2 Ab high positive sera, HSP 12- HIV-1 O Ab positive sera, HSP 13- HIV Ab and Ag negative sera

Table 10. Summary: The table shows summary of inter- run, inter-day, inter- site and inter-lot precision and reproducibility with % CV and SD COI

Results: The precision and reproducibility of the Elecsys HIV combi PT and Preci controls was acceptable, demonstrating only minor variability from run to run, day to day or reagent lot to reagent lot. The total CV for the panel members ranged below the acceptance criterion of 10%.

10.14. Reagent Stability Studies

10.14.1. Elecsys HIV combi PT and PreciControls reagents

- Reagent stability studies were carried out according to the protocol specifications for the Elecsys HIV combi PT reagents, PreciControl HIV Gen II and PreciControl HIV-2 + Grp O reagents and calibrators. The data for three lots show that the reagents of the Elecsys HIV combi PT and PreciControl HIV Gen II and PreciControl HIV-2 + Grp O are stable for 16 months when stored at 2- 8 °C.

- Temperature Stress Stability testing of the Elecsys HIV combi PT reagents was performed after temperature stress. Reagent kits were stored for (b) (4) at (b) (4) (stressed condition). Results showed that under the temperature stress conditions described above the Elecsys HIV combi PT recovery for HIV negative specimens was within (b) (4) and for HIV positive specimens within (b) (4) of the S/CO when stressed for (b) (4).

- Transport Stress Stability studies were conducted to determine the effect of elevated temperature on the Elecsys HIV combi PT during transportation. To assess the stability of the Elecsys HIV combi PT reagents after temperature stress during transport, reagent kits were stored for (b) (4) and for (b) (4) (hot weather conditions) and tested. Recovery levels of the specimens were calculated based on specimen to cutoff index (S/CO). Acceptable performance was observed for the reagent kit stressed (b) (4) at (b) (4) as well as for (b) (4) stressed at (b) (4).

- Reagent Stability studies after First Opening were performed to determine the time period over which the reagents (rack packs) can be kept at 2 - 8°C once opened were carried out. Results showed that the Elecsys HIV combi PT reagents were stable for 12 weeks at 2 - 8°C after first opening and the PreciControl reagents were stable for (b) (4) .

- Reagent On-Board Stability studies were performed to determine the time period in which the reagents can be kept on-board the analyzer once opened. Results showed that the Elecsys HIV combi PT reagents were stable for 28 days on-board the **cobas e** 602 analyzer at 20°C±2°C.

- Stability studies were performed to assess in use stability of the PreciControls on the **cobas e** 602 immunoassay analyzer. Results showed that the PreciControls were stable after reconstitution and storage at (b) (4)

10.15. Calibrator Stability Studies

- Calibrator Stability after First Opening: Studies were performed to determine the time period over which the Elecsys HIV combi PT calibrators can be kept at 2-8°C once opened. Results showed that the Elecsys HIV combi PT calibrators were stable for 12 weeks at 2 - 8°C after opening.

- On-Board Stability of Open Calibrators: Studies were performed to assess the on-board stability of the calibrators for the **cobas e** 602 immunoassay analyzer. Results showed that the Elecsys HIV combi PT calibrators were stable for (b) (4) on board the **cobas e** 602 immunoassay analyzer.

11. Summary of Clinical Studies

11.1. Clinical Specificity

Specimens from Low Risk Individuals

A multisite clinical study was performed to determine the specificity of the Elecsys HIV combi PT and compared with an FDA approved HIV assay. HIV confirmatory testing was performed using FDA approved HIV-1 Western Blot, HIV-2 EIA and HIV-1 RNA PCR tests, and research use-only HIV-2 Western Blot and HIV-1 p24 antigen assays. The specificity of the Elecsys HIV combi PT was determined in individuals who were at low risk for HIV infection. The low-risk population tested included 6050 specimens from low risk adults, 202 specimens from pregnant females negative for HIV, and 591 low risk pediatric subjects. The low risk cohort tested consisted of 50% plasma (3434/6843) and 50% serum (3409/6843) for a total of 6843 specimens. All specimens were prospectively collected. Of the 87 repeatedly reactive specimens, 83 were confirmed positive. Results are presented in Table 11:

Table 11.Elecsys HIV combi PT Reactivity in Low Risk Individuals

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Repeatedly Reactive Specimens (Number Positive by Method)				
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Adults (includes Pregnant women)	6050	5965	91	85	5960	92	90	83	2	0	0	0
Pediatric	591	589	3	2	591	0	0	0	0	0	0	0
Pregnant women negative for HIV	202	202	0	0	202	0	0	0	0	0	0	0
Total	6843	6756	94	87	6753	92	90	83	2[a]	0	0	0

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

a) Note: Two specimens with an inconclusive final diagnosis were counted against the Elecsys HIV combi PT and included in the calculation.

Table 11. Summary: The specificity of the Elecsys HIV combi PT assay in the low risk population was 99.94% (6754/6758) with a 95% confidence interval of 99.85% to 99.98%.

Results: Two specimens out of 6843 with an inconclusive final diagnosis, were non-reactive for the Elecsys HIV combi PT and were excluded from the calculation of specificity, reducing the numerator from 6756 to 6754 and the denominator from 6760 to 6758.The specificity of the Elecsys HIV combi PT assay in the low risk population was thus 99.94% (= (6841 subjects - 87 Elecsys HIV combi PT repeatedly reactive subjects) / (6841 subjects - 83 confirmed positives) = 6754/6758) with a 95% confidence interval of 99.85% to 99.98 %.

12. Clinical Sensitivity

12.1 Elecsys HIV combi PT Reactivity in Individuals Known to be Positive for Antibodies to HIV-1

A multi-site clinical study was performed to assess the sensitivity of the Elecsys HIV combi PT in 1460 individuals who were known to be HIV-1 antibody positive, including confirmed positive adults (symptomatic or asymptomatic), pediatric subjects, pregnant women positive for HIV, HIV-1 group M subtypes and HIV-1 p24 antigen/antibody positive subjects. All 1460 specimens were repeatedly reactive using the Elecsys HIV combi PT.

Table 12. Elecsys HIV combi PT Reactivity in Individuals Known to be Positive for Antibodies to HIV-1

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay		
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Adults -asymptomatic	820	0	820	820	0	820	820
Adults -symptomatic	205	0	205	205	0	205	205
Adults - non-US	200	0	200	200	0	200	200
Pediatric Population	50	0	50	50	0	50	50
Pregnant women	60	0	60	60	0	60	60
HIV-1 group M subtypes	75	0	75	75	0	75	75
p24+/antibody+	50	0	50	50	0	50	50
Total	1460	0	1460	1460	0	1460	1460

Table 12. Summary: The Elecsys HIV combi PT detected 1460 / 1460 specimens in the HIV-1 antibody positive cohorts.

Results: The sensitivity of the Elecsys HIV combi PT in the HIV-1 antibody positive cohort was 100.00% (1460/1460) with a 95% confidence interval of 99.75% to 100.00%.

12.2 Elecsys HIV combi PT Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

The sensitivity of the Elecsys HIV combi PT was determined in subjects who were from the Ivory Coast, Africa, known to be an HIV-2 endemic area. With the Elecsys HIV combi PT, 276 confirmed positive subjects were identified, including 211 subjects that tested positive on an HIV-2 Western Blot. All 211 specimens confirmed with an HIV-2 western blot are analyzed in Table 13, below:

Table 13. Elecsys HIV combi PT Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay		
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Known Positives for ab to HIV-2	211	0	211	211	0	211	211
Total	211	0	211	211	0	211	211

Table 13. Summary: The Elecsys HIV combi PT detected 211 of the 211 HIV-2 antibody positive specimens in the HIV-2 endemic cohort.

Results: The sensitivity of the Elecsys HIV combi PT in the HIV-2 antibody positive cohort was 100.00% (211/211) with a 95% confidence interval of 98.27% to 100.00%.

12.3 Elecsys HIV combi PT Reactivity in Specimens Positive for Antibodies to HIV-1 Group O

The sensitivity of the Elecsys HIV combi PT was determined in a multi-site study with specimens from individuals known to be positive for HIV-1 Group O based on certificate of analysis and/or from genetic sequencing provided prior to enrollment.

Table 14. Elecsys HIV combi PT Reactivity in Specimens Positive for Antibodies to HIV-1 Group O

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay		
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Group O	42	0	42	42	0	42	42
Total	42	0	42	42	0	42	42

Table 14. summary: The Elecsys HIV combi PT detected 42/42 specimens in the HIV-1 Group O cohort.

Results: The sensitivity of the Elecsys HIV combi PT in the HIV-1 Group O cohort was 100.00% (42/42) with a 95% confidence interval of 91.59% to 100.00%.

12.4 Elecsys HIV combi PT Reactivity with Specimens from High Risk Individuals

A total of 758 specimens from high risk adult, pediatric and pregnant subjects were tested with the Elecsys HIV combi PT in a multi-site study. The pediatric specimens were collected from subjects ranging in age from 2 to 21 years.

Table 15. Elecsys HIV combi PT Reactivity with Specimens from High Risk Individuals

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Repeatedly Reactive Specimens (Number Reactive / Positive by Method)				
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Adults	499	485	14	14	488	11	11	11	0	0	0	0
Pregnant	125	89	36	36	96	29	29	26	0	0	0	0
Pediatric	134	133	1	1	133	1	1	1	0	0	0	0
Total	758	707	51	51	717	41	41	38	0	0	0	0

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

Table 15. Summary: A total of 51//758 specimens from high risk individuals were repeatedly reactive using the Elecsys HIV combi PT assay, 41 were found to be repeatedly reactive with the FDA approved assay and 38 were confirmed to be positive by Western blot.

12.5 Elecsys HIV combi PT Reactivity in High Risk Individuals from an HIV-2 Endemic Region

A total 706 specimens from high risk subjects was tested using the Elecsys HIV combi PT in a multi-site study. These specimens were provided by a vendor and originated from Ivory Coast, known HIV-2 endemic region from Africa.

Table 16. Elecsys HIV combi PT Reactivity in High Risk Individuals from an HIV-2 Endemic Region

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Number Reactive / Positive by Method				
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
HIV-2 Endemic Area	706	421	286	285	422	284	284	237	275	1	1	211
Total	706	421	286	285	422	284	284	237	275	1	1	211

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

Table 16. Summary: One specimen out of 706 had an inconclusive final diagnosis and was non-reactive for the Elecsys HIV combi PT but reactive using the FDA approved assay. It was, therefore, excluded from the calculation, reducing the total number to 705. Of the 705 specimens tested, 285 were found to be repeatedly reactive using the Elecsys Combi PT assay, 284 were repeatedly reactive using the FDA approved assay, and 211 were confirmed to be positive by HIV-2 western blot.

12.6 Elecsys HIV combi PT Reactivity in specimens from Pregnant Females

A multi-site clinical study was performed to compare the performance of the Elecsys HIV combi PT to an FDA approved HIV assay using specimens from a pregnant population including HIV-positive, high risk and healthy pregnant females . Prospectively and retrospectively collected specimens from 440 pregnant women across all three trimesters were tested.

Table 17. Elecsys HIV combi PT Reactivity in specimens from Pregnant Females

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Number Reactive / Positive by Method				
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
HIV-Positive pregnant Females	25	0	25	25	0	25	25	25	0	0	0	0
High-Risk Pregnant Females	125	89	36	36	96	29	29	26	0	0	0	0
Healthy Pregnant	290[a]	290	0	0	290	0	0	0	0	0	0	0
Total	440	379	61	61	386	54	54	51	0	0	0	0

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

a) Note: The 290 Healthy Pregnant Females include 88 Low Risk Adults and 202 Pregnant Women Negative for HIV-1 .

Table 17. Summary: 25/25 specimens from HIV positive pregnant females were found to be positive using both the Elecsys combi PT assay and the FDA approved reference assay. Of 125 specimens tested from high risk females 36 were found to be repeatedly reactive using the Elecsys HIV combi PT assay and 29 using the FDA approved assay and 26 were confirmed by HIV-1 western blot. None of 290 specimens from healthy pregnant females were found to be reactive using both assays.

12.7 Elecsys HIV combi PT Reactivity in specimens from Pregnant Females at High Risk for Infection with HIV

A multi-site clinical study was performed to compare the performance of the Elecsys HIV combi PT to an FDA approved HIV assay using specimens from pregnant females at high risk for infection with HIV. A total of 125 specimens from all three trimesters were tested to determine the specificity in this cohort.

Table 18. Elecsys HIV combi PT Reactivity in specimens from Pregnant Females at High Risk for Infection with HIV

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay		
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**
First Trimester	18	11	7	7	11	7	7
Second Trimester	44	30	14	14	33	11	11
Third Trimester	63	48	15	15	52	11	11
Total	125	89	36	36	96	29	29

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

Note: The confirmatory tests performed on this cohort are shown above in Table 18

Table 18. Summary: Of 125 specimens tested 36 were repeatedly reactive using the Elecsys HIV combi PT assay and 29 were repeatedly reactive using the FDA approved assay.

12.8 Elecsys HIV combi PT Reactivity in Specimens from Pediatric population

A multi-site clinical study was performed to compare the performance of the Elecsys HIV combi PT with an FDA approved HIV assay using specimens from pediatric subjects. A total of 775 specimens, collected prospectively or retrospectively, were tested. The pediatric specimens included 591 low risk, 134 high risk and 50 known positive pediatric specimens. Specimens collected were in the age range of two to 21 years.

Table 19. Elecsys HIV combi PT Reactivity with Pediatric specimens

	Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Number Reactive / Positive by Method				
Specimen Population	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
Pediatric HIV Low Risk	591	589	3	2	591	0	0	0	0	0	0	0
Pediatric High-Risk	134	133	1	1	133	1	1	1	0	0	0	0
Pediatric HIV Positive	50	0	50	50	0	50	50	49 [b]	0	0	0	0
Total	775[a]	722	54 [a]	53[a]	724	51 [a]	51 [a]	50[b]	0	0	0	0

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

a) Includes 1 specimen with insufficient volume for confirmatory testing but which was positive based on the vendor's Certificate of Analysis and b) Excludes the one specimen with insufficient volume that was positive based on the vendor Certificate of Analysis

Table 19. Summary: 50/50 specimens from HIV positive pediatric patients were found to be positive using both the Elecsys HIV combi PT assay and the FDA approved assay.

Of 134 specimens from a high risk pediatric population, one was found to be repeatedly reactive using both Elecsys HIV combi PT and FDA approved assays and confirmed as positive by western blot. Of 591 specimens from a low risk pediatric population, 2 were found to be repeatedly reactive using the Elecsys HIV combi PT assay and none using the FDA approved assay but were negative on HIV-2 western blot. None of the specimens were repeatedly reactive using the FDA approved assay.

12.9 High Risk Pediatric Specimens Categorized by Age Range and Gender

A multi-site clinical study was performed to compare the performance of the Elecsys HIV combi PT with an FDA approved HIV assay using specimens from high risk pediatric subjects. A total of 134 specimens, collected prospectively were tested. Results categorized by age range and gender are shown below in Table 20:

Table 20. Distribution of High Risk Pediatric Specimens Categorized by Age Range and Gender

		Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Number Reactive / Positive by Method				
Age	**Sex**	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
2 to 5 years	Female	2	2	0	0	2	0	0	0	0	0	0	0
2 to 5 years	Male	2	2	0	0	2	0	0	0	0	0	0	0

		Elecsys HIV combi PT Assay				FDA Approved HIV Assay			Number Reactive / Positive by Method				
Age	**Sex**	**N**	**NR**	**IR**	**RR**	**NR**	**IR**	**RR**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**	**HIV-2 Western Blot**
6 to 10 years	Female	4	4	0	0	4	0	0	0	0	0	0	0
6 to 10 years	Male	4	4	0	0	4	0	0	0	0	0	0	0
11 to 15 years	Female	8	8	0	0	8	0	0	0	0	0	0	0
11 to 15 years	Male	6	6	0	0	6	0	0	0	0	0	0	0
16 to 21 years	Female	63	63	0	0	63	0	0	0	0	0	0	0
16 to 21 years	Male	45	44	1	1	44	1	1	1	0	0	0	0
Total		134	133	1	1	133	1	1	1	0	0	0	0

N=Number tested, NR= Non – reactive, IR= initially reactive, RR= repeatedly reactive

Table 20. Summary: The Elecsys HIV combi PT assay and the FDA approved HIV assay were reactive in 1/134 specimens in the pediatric population in different age and gender groups at high risk for HIV infection.

13. Inspections

13.1. Manufacturing Facilities Review/Inspection

Roche Diagnostic GmbH in (b) (4) has been recently inspected multiple times for CDER and CDRH in-vitro diagnostic products. The registration number (b) (4) is active for the facility and the FEI # is (b) (4). As the assay will be approved under the regulations for a PMA and not a BLA, no license number is assigned.

Roche Diagnostic GmbH in Mannheim, Germany has been recently inspected multiple times for CDER and CDRH in-vitro diagnostic products. The registration number (9610126) is active for the facility and the FEI # is 3002806559. As the assay will be approved under the regulations for a PMA and not a BLA, no license number is assigned.

Based on the information provided in the PMA submission, and the previous inspection reports supporting the overall compliance status of the manufacturing sites, the review committee recommended waiving the pre-approval inspections for the facilities associated with this PMA.

13.2 Bioresearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments at the two testing sites in the United States. These inspections did not reveal significant problems that impact the data submitted in this PMA. The inspections were classified as No Action Indicated (NAI).

14. Conclusions Drawn from the Studies

14.1. Risk/Benefit Analysis

As a diagnostic test the Roche Elecsys HIV combi PT assay involves removal of blood from an individual for testing purposes. This test presents no more of a safety hazard to an individual than is presented to an individual who is having their blood drawn for any other diagnostic evaluation. The benefit to HIV-1 or HIV-2 infected individuals tested by this assay outweighs any potential adverse event or risk to the patient or user due to assay malfunction or operator error. The potential risks encountered with this in vitro diagnostic test are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for these devices. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user. Potential adverse effects of the Roche Elecsys HIV combi PT assay relate to the risk of false positive and false negative results. While performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exists. The risk of incorrect results is minimized by following the procedures and instructions outlined in the Package Insert.

14.2 Safety and Effectiveness

Multi-centered clinical studies were conducted in the US. The Roche Elecsys HIV combi PT Assay performed with clinical sensitivity and specificity comparable to a FDA approved HIV Ab assay. Results from the clinical studies indicate that the Roche Elecsys HIV combi PT assay, together with supplemental testing, can be used safely and effectively for the qualitative in vitro detection of HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody and HIV-1 Group O antibody in human serum and plasma. Reactive specimens must be investigated by additional, more specific, or supplemental tests. Both confirmation of the test result on a freshly drawn specimen and counseling are considered an important part of testing for HIV antigen and antibody to HIV-1 and HIV-2. A negative test result at any point in the investigation of individual subjects does not preclude the possibility of exposure to or infection with HIV-1 and/or HIV-2. Negative results can occur if the quantity of marker present in the specimen is below the detection limit of the assay, or if the marker is not present during the stage of disease in which a specimen is collected.

The safety and effectiveness of the Roche Elecsys HIV combi PT assay has been shown in the clinical and non-clinical studies performed. The assay has been shown to be an effective tool in detecting infection with HIV-1 or HIV-2.

15. PANEL RECOMMENDATIONS (TO BE COMPLETED BY FDA)

N/A

16. CBER DECISION (TO BE COMPLETED BY FDA)

Approved