Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Summary Basis for Regulatory Action

Date:	October 16, 2023
From:	Iwona Fijalkowska, Ph.D., Chair of the Review Committee
BLA/ STN#:	125792/0
Applicant Name:	Roche Diagnostic Solutions 9115 Hague Road; Indianapolis, IN 46256
Date of Submission:	December 22, 2022
MDUFA Goal Date:	October 20, 2023
Proprietary Name:	Elecsys HTLV-I/II PreciControl HTLV PreciControl Release HTLV

Established Name (common or usual name): Elecsys HTLV-I/II test for use with **cobas pro** serology solution comprising of **cobas e** 801 analytical unit and **cobas pro** serology controller.

Intended Use/Indications for Use:

Elecsys HTLV-I/II is an in vitro immunoassay for the qualitative detection of antibodies to HTLV-I and HTLV-II in human serum and plasma. Elecsys HTLV-I/II is intended to screen individual human donors, including volunteer donors of whole blood and blood components. The assay 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**mmunoassa**y** "ECLIA" is intended for use with **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.

Recommended Action: The Review Committee recommends licensure of this product.

Review Office Signatory Authority: Anne Eder, MD, PhD; Director (Acting), Office of Blood Research and Review

□ **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.**

Summary Basis for Regulatory Action

The table below indicates the material reviewed when developing the SBRA.

Table 1: Reviews Submitted

Document Title	Reviewer Name	Document Date
Product Review (*OBRR/DETTD*) • *Clinical* • *Non-Clinical*	 Iwona Fijalkowska Viswanath Ragupathy Virginie Dujols Kavita Singh Xue Wang	 10/10/2023 06/12/2023 07/18/2023 08/23/2023 06/15/2023
Statistical Review • *Clinical and Non-Clinical (OBPV/DB/DNCE)*	Paul Hshieh	08/25/2023
CMC Review • *CMC (OBRR/DETTD)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DBSQC)* • Establishment Inspection Report(s) (*OCBQ/DMPQ*)	 Krishnakumar Devadas Nitin Verma Alifiya Ghadiali Prajakta Varadkar Simleen Kaur Alifiya Ghadiali Prajakta Varadkar	 07/26/2023 09/07/2023 06/22/2023 10/11/2023 09/26/2023 07/13/2023 10/11/2023
Labeling Review(s) • *OBRR* • *APLB (OCBQ/APLB)*	 Iwona Fijalkowska Sadhna Khatri	 10/11/2023 07/11/2023
Lot Release Protocols/Testing Plans/Testing Panel (*OCBQ/DBSQC*)	George Kastanis Matthew Arnold	08/07/2023 10/12/2023
Bioresearch Monitoring Review (*OCBQ/BIMO*)	Malcolm Nasirah	05/5/2023
Software and Instrumentation (*OBRR/DETTD*)	Rana Nagarkatti Hongqiang Hu	09/12/2023 09/8/2023
Other living donor and cadaveric claim (OTP/DHT)	Hanh Khuu	09/11/2023

Summary Basis for Regulatory Action

1. Introduction

The Elecsys HTLV-I/II assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4), Germany. This biologics license application (BLA) for Elecsys HTLV I/II assay from Roche Diagnostics Solutions, 9115 Hague Road Indianapolis, IN 46250, USA was received on December 21, 2022.
The application was assigned the number STN 125792/0 and granted a standard 10-month review status with a goal date of October 21, 2023. The application was filed February 21, 2023, and the mid-cycle meeting took place on May 18, 2023.

The BLA application was preceded by pre-submission BQ170139/0 and a series of five supplements BQ170139/1 to BQ170139/5, focused on the regulatory aspects related to software and instrumentation, pre-clinical studies as well as clinical studies for a group of Elecsys assays planned by Roche to be submitted to FDA for approval. The Elecsys assays are intended for use with the **cobas e** 801 analyzer and **cobas pro** serology solution. Due to commonalities between the technology and assay formats, an investigational new drug application (IND) 27257 was submitted collectively for all planned assays, followed by thirteen amendments; the last amendment was dated December 21, 2022.

Table 2: Chronological Summary of Submission and FDA Interaction with Roche Diagnostics (RD)

Date	Action	Amendment to BL125792
December 21, 2022	BLA application receipt	
December 28, 2022	Acknowledgement Letter	
February 21, 2023	Filing Notification Letter	
Feb 13, 2023	FDA IR: Consolidated request for CMC Bioburden and (b) (4) testing and information on clinical testing sites	
March 20, 2023	Response to IR dated Feb 13, 2023 on Bioburden testing clinical sites	/0/1
April 03, 2023	FDA IR: Bioburden testing- follow up	
April 18, 2023	Response to IR dated April 03, 2023 on time frame for bioburden testing	/0/2
May 04, 2023	FDA IR: Bioburden testing follow-up and analytical testing	

Summary Basis for Regulatory Action

May 09. 2023	Roche submitted an Amendment for updating the serology controller software from version 1.0.3 to version 1.1.	/0/3
May 17, 2023	FDA IR: Missing information on clinical sites, in FDA Form 356	
May 18, 2023	Response to IR dated May 17, 23: Roche submitted corrected FDA Form 356h	/0/9
May 19, 2023	Response to IR dated May 04, 2023: Roche provided requested analytical data	/0/4
May 24, 2023	FDA IR: Request for a Lot Release Protocol Template	
May 31, 2023	Response to IR dated May 24, 23: Roche submitted a Lot Release Protocol Template	/0/5
June 06, 2023	FDA IR: Request for information on the source material	
June 13, 2023	Response to IR dated June 06, 2023: Roche submitted information on the source material	/0/6
June 14, 2023	FDA IR: Information on Lot Release Panel testing site	
June 15, 2023	Roche response to IR dated June 14, 2023: information on the Lot Release Panel testing site	/0/7
June 29, 2023	FDA IR: Additional information on source materials for positive and negative HTLV assay calibrators and controls	
July 05, 2023	Roche response to IR dated June 29, 23 on source materials	/0/10
July 06, 2023	FDA IR: Value assignment protocols for positive calibrator and control materials	
July 12, 2023	Roche response to IR dated July 06, 23: provided value assignment protocols	/0/11
July 25, 2023	FDA IR: Drug interference	
July 26, 2023	FDA IR: Lot Release Protocol Template, follow up	

July 27, 2023	Response to IR dated July 25, 23: final Bioburden verification report. Also, a follow up response to IR dated June 29, 23 on analytical and clinical studies	/0/12 /0/13
July 31, 2023	Response to IR dated July 26, 23	/0/14
July 31, 2023	FDA: The HTLV blinded panels were submitted to Roche	
August 14, 2023	FDA IR for clarification on the sample size in the sample on-clot stability study (non-clinical)	
August 17, 2023	Roche response to IR dated August 14, 2023	/0/15
August 30, 2023	Roche response: Lot Release Panel results	/0/16
September 22, 2023	FDA IR for labeling updates to harmonize with other Elecsys assays labeling	
September 27, 2023	FDA IR regarding matrix equivalence study	
September 29, 2023	Roche response to IR dated September 27, 2023 on matrix equivalence study	/0/17
September 29, 2023	Roche response to IR dated September 27, 2023 on Elecsys HTLV-I/II labeling	/0/18

2. Background

The Elecsys HTLV-I/II is a qualitative serologic sandwich immunoassay intended for detection of antibodies to HTLV-I and HTLV-II in human serum and plasma. The antibodies are detected using HTLV-specific recombinant antigens HTLV-I gp21 and HTLV-II gp24, and the detection is based on the electrochemiluminescence immunoassay (ECLIA) principle. Additional controls, calibrators and general use reagents are also required to perform the assay and described in the CMC section below.

This assay is designed to be performed on the **cobas e** 801 instrument, a high throughput, fully automated immunoassay analyzer that provides routine and priority processing while allowing continuous access and automated retesting. The **cobas e** 801 Immunoassay Analyzer Instrument incorporates a dedicated software package for instrument control, data collection, results analysis, calibration, quality control, and service software. Results are determined automatically by the Elecsys software based on the comparison of the electrochemiluminescence signal of the sample to the signal obtained by an

HTLV calibration. The result of a sample measurement is given either as reactive or non-reactive, as well as in the form of a cutoff index (COI; signal sample/cutoff). Samples with a COI <1.00 are considered non-reactive for HTLV-I/II specific antibodies and do not need further testing. Samples with a COI ≥1.00 are considered initially reactive on the Elecsys HTLV-I/II. All initially reactive samples are automatically retested in duplicate using the Elecsys HTLV-I/II assay. Validation of all results is based on test result batches that are concluded by successful release control measurements.
The **cobas pro** serology solution is intended for use only with licensed blood screening assays by U.S. blood banks and plasma fractionators. It is intended for use only by personnel who are trained in its operation. Detailed device description is provided in the CMC and Software and Instrumentation sections below.

3. Chemistry Manufacturing and Controls (CMC)

The manufacture of the Elecsys HTVL-I/II assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Elecsys HTLV I/II assay is manufactured at the Roche Diagnostics GmbH facilities in Germany located at (b) (4) Sandhofer Strasse 116, Mannheim, 68305, Germany. The (b) (4) site is located at Roche Diagnostics Operations 9115 Hague Road Indianapolis, IN 46250, USA.

The Elecsys HTLV-I/II test kit (List Number 09015272162) consists of 20 reagent cassettes (**cobas e** pack), each containing components M, R1, and R2; and two identical calibrator packs, each containing the components HTLVB Cal1 and HTLVB Cal2. The kit components are listed below:

- Component M: Streptavidin coated microparticles for capturing biotin-complex
- Components R1 and R2: R1 (biotinylated-) and R2 (ruthenylated-) HTLV-I gp21 and HTLV-II p24 recombinant antigens
- HTLVB Cal1: Non-reactive calibrator 1, human serum negative for HTLV antibody
- HTLVB Cal2: Reactive calibrator 2, human serum positive for HTLV antibody

PreciControl HTLV (List Number 07108133162), supplied separately, is used for quality control of Elecsys HTLV-I/II. The control kit consists of the following components:

- PC HTLV0 B: Negative control, human serum non-reactive for anti-HTLV-I or II antibodies
- PC HTLV1 B: Positive control, human serum reactive for anti-HTLV-I antibodies
- PC HTLV2 B: Positive control, human serum reactive for anti-HTLV-II antibodies

PreciControl HTLV Release (PC HTLVR; List Number 09366989190), identical to PC HTLV1 B, supplied separately, is used as a release control and consists of the human serum reactive for anti-HTLV antibodies identical to PC HTLV1 B.

Other general-purpose reagents and consumables for **cobas e** 801 analyzer used for processing all Elecsys assays are listed below:

- AssayTip/AssayCup tray (List Number 05694302001): Disposable pipetting tips and reaction vessels.
- CleanCell M (List Number 04880293190): Cleaning solution for the measuring cell.
- ISE Cleaning solution/Elecsys SysClean (11298500160): System cleaning solution
- Liquid Flow Cleaning Cup (List Number 07485425001): Cups to supply ISE Cleaning Solution/Elecsys SysClean.
- PreClean II M (List Number 06908853190): Wash solution.
- PreWash Liquid Flow Cleaning Cup (List Number 07485433001): Cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit.
- ProCell II M (List Number 06908799190): System reagent for generating electrochemical signal
- Reservoir cup (List Number 07485409001): Cups to supply ProCell II M and CleanCell M solutions.

b) Testing Specifications

The analytical methods and their validations and/or qualifications were reviewed for the Elecsys HTLV-I/II assay and found to be adequate for their intended use.

c) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d) Facilities Review/Inspection

Summary Basis for Regulatory Action

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The activities and inspectional history for each facility involved in the manufacture of Elecsys HTLV-I/II are presented in the table below (Table 3) and summarized.

Table 3. Manufacturing facilities for Elecsys HTLV I/II

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification /Results
Roche Diagnostics GmbH (b) (4) *Manufacturing of Elecsys kit components and Control reagents. Release testing of final device (assay).*	(b) (4)	(b) (4)	Waived	CDER Pre-License Inspection (b) (4); VAI ORA Post-Market Approval Inspection (b) (4); NAI
Roche Diagnostics GmbH Sandhofer Strasse 116, 68305 Mannheim, Germany *Labeling and final assembly of Elecsys HTLV-I/II kit and PreciControl. Manufacturing, labeling and packaging of system reagents.*	3002806559	315028860	Waived	MRA Inspection Review by ORA/OPQO October 2021; VAI ORA For-Cause Inspection August 2019; VAI ORA Post-Market Approval Inspection April 2018; NAI

MRA – Mutual Recognition Agreement; NAI – No Action Indicated; ORA – Office of Regulatory Affairs; OPQO – Office of Pharmaceutical Quality Operations; VAI – Voluntary Action Indicated.

Roche Diagnostics GmbH, (b) (4)

(b) (4): The Center for Drug Evaluation and Research conducted a pre-license inspection at Roche Diagnostics GmbH, (b) (4) in (b) (4). The inspection covered the Warehouse and the Quality Control Laboratories associated with the subject BLA. All FDA Form-483 issues were

resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

(b) (4) : Office of Regulatory Affairs (ORA) performed a post-market approval inspection. This inspection covered the Management Controls, Corrective Actions and Preventive Actions, Production & Process Controls, and Design Controls associated with the subject BLA. No FDA Form-483 was issued and the inspection was classified as No Action Indicated (NAI).

2018-2023: ORA review and a records request were performed. The inspection was conducted under Mutual Recognition Agreement (MRA). The review covered drug substance and drug product regulated by CDER and was classified as either VAI or NAI.

Roche Diagnostics GmbH, Mannheim, Germany

October 2021: The Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations performed a review of a foreign surveillance inspection under the Mutual Recognition Agreement. Manufacturing operations covered during the inspection included sterile products and biological medicinal products, packaging and quality control testing. A GMP certificate is available in the European Union Drug Regulatory Authorities Network database. This inspection was classified as VAI.

August 2019: ORA performed a for-cause inspection. FDA Form-483 issues were resolved and the inspection was classified as VAI.

April 2018: ORA performed a post-market approval inspection for CDRH regulated Elecsys Class 3 assays. No FDA Form-483 was issued and the inspection was classified as No Action Indicated.

Additional inspection was performed for a drug product regulated by CDER; inspection was classified as VAI.

e) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

f) Container Closure

The assay components are packaged in plastic bottles with plastic snap caps. The calibrators and controls are packaged in glass bottles with rubber stoppers and plastic screw caps. The system reagents are packaged in either plastic bottles with plastic screw caps or dropper bottle with dropper and plastic screw cap.

Container closure integrity is not assessed as all products are manufactured as bioburden controlled and contain preservatives.

4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

a) Versioning

cobas pro serology controller version 1.1.0, **cobas pro** core software version 02-01, and **cobas pr**o serology solution User Guide version 1.5.

b) Device Description: cobas pro serology solution

The **cobas pro** serology solution is a combination of the **cobas pro** serology controller (software), **cobas pro** integrated solutions (with up to four **cobas e** 801 analytical units with hardware and system software) and applicable licensed blood screening assays (**cobas e** flow and associated parameters and testing requirements for each assay). All software components of the Roche Serology Solutions meet the definition of Major Level of Concern due to their application in blood donor screening and the release of blood or blood components for transfusion or further manufacture. The **cobas pro** integrated solutions (**cobas pro**) is a fully automated system for the measurement of analytes in blood and its modular design allows for different combinations/ configurations of analytical units (e.g., **e** 801, **e** 602 or **e** 402).

The **cobas pro** automates electrochemiluminescence immunoassay test processing, result interpretation, and data management functions for screening of donations of whole blood and blood components using plasma or serum samples. For blood donor screening, each **cobas pro** integrated solutions configuration consists of up to four **cobas e** 801 analytical units. The **cobas e** 801 is a fully automated immunoassay analyzer intended to perform high throughput routine and priority testing (300 tests/hour) while allowing continuous access and automated retesting. The **cobas e** flow assay specific software modules, assay specific parameters included in the Application Code Numbers (ACN) and in the method sheets, control processing of each assay type on the **e** 801 analyzer. Positive sample ID is established and maintained with barcodes. Consumables are tracked for availability, stability and expiration using barcodes and RFID chips. The **cobas pro** serology solution interfaces

with Laboratory Information Systems (LIS) for order and result reporting, it monitors the operation of up to four **cobas pro** integrated solution with **cobas e** 801 analyzers, validates results, stores, and archives data, and maintains assay calibration status. **cobas pro** serology solution also interfaces via **cobas** link for data transfer between the laboratory and the **cobas e**-library, to view and synchronize data from method sheets, value sheets for calibrators and controls, and other reagent documents, including test-specific system parameter files, lot-specific application parameter files, and calibrator and QC parameter files. This data is automatically downloaded to analyzers based on kit barcodes and RFID tags. Additional system functionalities and operation are described in the version-controlled user manual, method sheets and package inserts.

c) Risk Management

Risks related to donor test results, exposure of user to infectious disease agents, chemical, physical and environmental hazards were evaluated. Major hazards include incorrect results, i.e., false positive and false negative donor test results, and moderate hazards include delayed results and physical hazards to the user/operator. The final risk profile of the **cobas e** 801 analyzer includes 0 red (unacceptable) risks, 15 yellow risks (that required assessment of acceptability), and 242 green (acceptable) risks. Of the 15 yellow risks, four are related to false negative results (due to wrong consumables placement, incorrect instrument processing, and non-conforming lab facilities), one is related to false positive results (due to incorrect instrument processing; for competitive assays only and irrelevant to the Elecsys HTLV-I/II test results) and 10 are related to a use of **cobas e** 801 analyzer (due to user exposure to infectious material, personal injury leading to delays/interruption). The final cybersecurity risk profile of the **cobas pro e** 801 analyzer includes 0 red risks, 19 yellow risks, and 79 green risks. The final risk profile of the **cobas pro** serology solution includes 0 red risks, 0 yellow risks and 24 green risks. The final cybersecurity risk profile of the **cobas pro** serology solution includes 0 red risks, 19 yellow risks, and 25 green risks. There were 0 red or yellow risks for the Elecsys HTLV-I/II assay, PreciControls and accessories needed to perform the assay.

The applicant stated that all risk control measures are implemented and verified, and that the labeling notifies the user of residual risks. Significant risk control measures include use of barcodes/RFID tags for sample and reagent tracking, automated checks for expiry of onboard assay reagents and QC reagents, maintenance procedures, labeling and user manuals, database management with automated scheduled data backups, and access controls with individual usernames and passwords, automated lock-out after periods of inactivity, firewalls and encryption, and configuration management, among others. The applicant concluded the overall residual risk of the **cobas pro**

serology solution is acceptable. This assessment appears to be supported by the evidence provided.

d) Unresolved Anomalies

The **cobas pro** serology controller version 1.1.0 contains 45 non-safety-related open anomalies with minor severity and no patient risks identified, and 24 open anomalies assessed as causing minor user annoyance with minimal impact on testing. The **cobas pro e** 801 instrument software version 02-01 contains 43 non-safety-related open anomalies with minor severity and no patient risks identified.

e) Testing

Design verification was performed to confirm that the design elements meet the specified requirements and includes verification of the effectiveness of risk control measures for potential causes of failure modes. This included software verification, software validation, testing at the unit level for each functionality and detailed integration testing for all functions and system level integration. Test run results using representative assays and donor samples were provided. System integration testing confirmed that the **cobas pro** serology solution met requirements using the Elecsys HBsAg and HTLV-I/II assay reagents and assay files, and instrument accessories.

f) Development Management

The software development activities for each software component included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation, defects tracking, configuration management, and maintenance activities to ensure the software conforms to user needs and intended uses.

g) Versioning

cobas pro serology controller version 1.1.0, **cobas pro** core software version 02-01, and **cobas pro** serology solution User Guide version 1.5.

Review Note: As agreed in BQ10139/1, Roche submitted a software update for the Serology Controller software from version 1.0.3 to 1.1.0. The update includes automation of the onboard stability and usage tracking of calibrator/control material, and improvements from usability studies. The update does not change critical assay specific parameters such as volumes of reagents used, time for incubations, or time to signal readout. Thus, clinical data acquired using software version 1.0.3 and submitted for review in the current application for Elecsys HTLV-I/II are not impacted by this update.

Summary Basis for Regulatory Action

5. Analytical Studies

Non-clinical studies were performed at Roche Diagnostics GmbH, (b) (4) . The analytical studies were conducted in compliance with 21 CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

a) Precision Studies

Precision of the Elecsys HTLV-I/II assay was evaluated at one site with one instrument and one lot of Elecsys HTLV-I/II assay and one lot of PreciControl HTLV. The samples were tested over 21 days, with one run per day, using four replicates, yielding n=84 measurements per sample. The member panel included:

- One HTLV antibody negative specimen at target level COI (b) (4)
- Two HTLV antibody high-negative specimens at target level COI (b) (4)
- One HTLV antibody low positive sample at the target COI (b) (4)
- One HTLV antibody positive sample at the target COI (b) (4)
- One HTLV antibody positive sample at the target COI (b) (4)
- PreciControl HTLV0 at target level COI (b) (4)
- PreciControl HTLV 1 at COI (b) (4)
- PreciControl HTLV 2 at target COI (b) (4)

Table 4: Intermediate (Within-Laboratory) Precision for Elecsys HTLV-I/II

Sample	Mean COI	N	Repeatability		Within-Laboratory Precision	
			SD	CV [%]	SD	CV [%]
HSP 1	0.100	84	0.001	1.2	0.001	1.7
HSP 2	0.968	84	0.013	1.4	0.022	2.3
HSP 3	0.906	84	0.012	1.3	0.020	2.2
HSP 4	1.12	84	0.015	1.3	0.026	2.4
HSP 5	5.88	84	0.081	1.4	0.165	2.8
HSP 6	25.5	84	0.477	1.9	0.799	3.1
PC HTLV0	0.101	84	0.002	20.	0.002	2.2
PC HTLV1	5.37	84	0.096	1.8	0.135	2.5
PC HTLV2	2.79	84	0.045	1.6	0.073	2.6

* HSP=Human Specimens; PC= PreciControls; N = number of replicates; CV = coefficient of variation expressed as a percentage ((CVs are not meaningful when S/CO approaches zero); SD = standard deviation

b) Limit of Detection

(b) (4)

(b) (4)

c) Endogenous Interferences (Spiked)

Assay performance was evaluated in samples with high levels of spiked interferents (hemoglobin, lipemia, bilirubin, and human serum albumin for total protein) using matched sets of analyte-negative, analyte low positive ((b) (4) S/CO) and positive ((b) (4) S/CO) donor serum specimens spiked with interferents. (b) (4) The data demonstrate acceptable performance of the assay for both nonreactive and reactive samples, supporting the use of the Elecsys HTLV-I/II with donor specimens containing up to (b) (4) mg/dL of hemoglobin, (b) (4) mg/dL lipid, (b) (4) mg/dL bilirubin, and (b) (4) g/dL of total protein. In addition, a negative control, and high, medium, and low positive samples were spiked with biotin, where the highest concentration tested was (b) (4) ng/mL and tested for interference. No interference was observed up to a biotin concentration of (b) (4) ng/mL.

d) Endogenous Interferences (Native)

Assay performance when used to test specimens containing naturally occurring elevated levels of hemoglobin, triglycerides, bilirubin, human serum albumin, and rheumatoid factor were evaluated. (b) (4) HTLV-I/II negative serum and plasma specimens for each interferent were used. No false reactive results were obtained. The data provided and reviewed demonstrate acceptable performance of the assay supporting use of specimens that contain up to (b) (4) of hemoglobin, (b) (4) of triglycerides, (b) (4) of total bilirubin, (b) (4) of total protein, and (b) (4) rheumatoid factor (range tested (b) (4)).

e) Analytical Sensitivity

The analytical sensitivity was not tested due to lack of the recognized standard and lack of relevant sample panels. The sensitivity is demonstrated by Limit of Blank (LoB) and Limit of Detection (LoD).

Summary Basis for Regulatory Action

f) Cross Reaction/Analytical Specificity

Analytical specificity of the Elecsys HTLV-I/II assay was evaluated by testing specimens with conditions or disease states unrelated to HTLV infection. Samples containing potentially interfering factors (n=248 samples) were spiked individually with anti-HTLV-I or anti-HLTV-II antibodies and the effect of potentially interfering factors was tested. The following specimens were used:

- Containing antibodies against HAV IgM, HAV IgG, HBV (acute and chronic), HCV, HIV, HSV 1, HSV 2, EBV IgM/IgG, CMV, Rubella, VZV
- Containing autoantibodies (ANA), Heterophilic antibodies (HAMA), elevated titers of rheumatoid factor (RF)
- Positive for antibodies against Candida albicans, Chlamydia, *E. coli*, Toxoplasma gondii, Treponema pallidum (syphilis)
- After vaccination against influenza
- From persons with Hyper IgG and Hyper IgM
- From pregnant women and multiparous pregnancies

The obtained data demonstrated acceptable performance of the assay and indicate that the presence of potentially interfering substances or medical conditions included in the study has no effect on the detection of anti-HTLV-I and anti-HTLV-II antibodies. There was no significant effect on background signals in negative specimens (neat specimens).

g) Drug interference

Potential interference with the Elecsys HTLV-I/II assay from common therapeutic drugs was tested using HTLV-I/II negative and positive samples spiked individually with the following drugs: (b) (4) No interference with Elecsys HTLV I/II assay was detected from the drugs tested.

h) Prozone (Hook Effect)

Assay performance was evaluated using high-titer, HTLV positive samples (from COI (b) (4) to COI (b) (4)) undiluted and diluted, with a dilution factor ranging from (b) (4) . The study demonstrated the absence of hook effect.

i) Serum and Plasma Comparison

The impact of anticoagulants on the performance of the Elecsys HTLV-I/II assay was evaluated using (b) (4) matched serum and plasma specimens collected from individual HTLV donors. Reactive samples and near cut-off non-reactive samples were contrived by collecting (b) (4) individual non-reactive donor samples and

spiking each with material from pooled reactive donor samples collected from (b) (4) unique reactive samples in a ratio ranging from (b) (4) volume of the reactive material in the final sample to achieve a range of (b) (4) COI to (b) (4) COI. (b) (4) negative samples were tested from unique native samples.

The assay performance when used with samples anticoagulated with Lithium heparin, Sodium citrate, di-Potassium EDTA, tri-Potassium EDTA and CPD was compared to the performance demonstrated when testing serum specimens. In addition, the suitability of different blood collection tubes was evaluated by testing samples collected with serum-, K2-EDTA- and lithium heparin-separation tubes. The data provided and reviewed demonstrate acceptable performance of the assay with specimens collected in the anticoagulants and tube types listed above supporting the use of specimens collected in these anticoagulants and tube types.

j) Specimen Storage

Assay performance with serum specimens and plasma specimens collected in K2- EDTA, Sodium Citrate, Li-Heparin and CPD stored at various temperatures for different periods of time was evaluated using serum and plasma specimens. The target analyte concentrations ranged from (b) (4) to (b) (4) COI for negative and from (b) (4) COI to (b) (4) COI for HTLV positive samples.

The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of serum and plasma specimens that were stored at approximately 15 to 30°C for up to (b) (4) days, 2 to 8°C for up to (b) (4) days, -20°C or colder for up to (b) (4) months, and up to (b) (4) freeze/thaw cycles. These data support the storage claims in the package insert.

k) Specimen Processing

Assay performance with centrifuged non-frozen and previously frozen specimens was evaluated using (b) (4) serum specimens— HTLV negative (n=(b) (4)) or spiked with HTLV-I and HTLV-II (n=(b) (4)) low positive and with HTLV-I (n=(b) (4)) and HTLV-II high positive (n=(b) (4)) — compared to the uncentrifuged, homogenized reference. The target concentrations ranged from (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of the assay with non-frozen and previously frozen serum specimens when centrifuged for 10 to 15 minutes at 2000 to 4000 RCF (relative centrifugal force = x g).

l) On-clot Specimen Processing

Assay performance with serum and plasma (di-Potassium EDTA, Sodium Citrate, and Lithium Heparin) specimens after storage on-clot was evaluated using (b) (4)

specimens across all specimen types— HTLV-I/II negative (n=(b)(4)) and HTLV-I/II low and high positive (n=(b)(4)) and compared to specimens stored at unstressed conditions. The target concentrations ranged from (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of the assay with samples stored on-clot for 7 days at 15 to 30°C and 14 days at 2 to 8°C.

m) Kit Lot Calibration and On-Board Calibration Stability

Calibration of the Elecsys HTLV-I/II assay must be performed once per reagent lot using HTLVB Cal1, HTLVB Cal2 and fresh reagent. Lot calibration stability was validated using Elecsys HTLV-I/II kit of the same lot stored a 2 to 8°C up to (b)(4) weeks using the initial calibration. A total of (b)(4) serum specimens—HTLV-I/II negative (n=(b)(4)) and spiked (n=(b)(4)) at analyte level range (b) (4) S/CO along with (b) (4) PreciControls—were tested in (b) (4) and compared to unstressed reagents of the same lot measured using the initial calibration. The data provided and reviewed demonstrate acceptable performance of the assay supporting a Lot Calibration stability of up to 12 weeks. In addition, the same panel and acceptance criteria were utilized to test stability of the Elecsys HTLV-I/II kit components stored on-board a **cobas e** 801 analyzer for 28 days with panel test results obtained using the initial calibration. Acceptable performance was observed, supporting the On-Board stability of up to 28 days using the initial calibration.

n) Reagent Stability Studies

Reagent real time stability was determined using (b) (4) Elecsys HTLV-I/II kit lots stored at 2 to 8°C up to (b)(4) months compared to t = 0 months. A total of (b)(4) serum specimens at (b) (4) reactivity levels ((b) (4)) along with the PreciControls were tested in (b) (4) and compared to unstressed reagents. The data provided and reviewed demonstrate acceptable performance of the assay supporting a reagent stability claim of up to 15 months at 2 to 8°C. A sample panel of (b)(4) serum specimens at the reactivity range (b) (4) S/CO was utilized to evaluate on-board stability of the Elecsys HTLV-I/II kit components when stored at (b) (4) for (b)(4) weeks. Transport stability was evaluated at (b) (4) for (b) (4) when compared to unstressed kits stored at 2 to 8°C to evaluate stability during shipping. Acceptable performance was observed, supporting an on-board stability claim of up to 16 weeks at (b) (4) and a transportation claim of up to (b) (4).

o) Temperature Effects on Samples, Calibrators and PreciControls Prior to Measurement

Assay performance with specimens, calibrators, and controls directly after storage at 2 to 8°C was evaluated using (b)(4) serum specimens—HTLV-I/II negative (n=(b)(4)) or spiked at (b) (4) reactivity levels with HTLV-I and HTLV-II antibody — and compared

with samples that were equilibrated at (b) (4). The target concentrations obtained ranged from (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of specimens and kit components without first equilibrating at for (b) (4).

p) Calibrator Stability

Stability of reconstituted calibrators was evaluated by measuring them in (b) (4) after storage under various conditions. The data provided and reviewed demonstrate acceptable performance of calibrators supporting stability claims of storage for 5 hours at 20°C to 25°C after reconstitution, up to (b) (4) days at 2°C to 8°C, up to (b) (4) at (b) (4), and up to (b) (4).

q) PreciControl Stability

Stability of lyophilized PreciControl (PC) HTLV0 B; PC HTLV1 B and PC HTLV2 B was validated after storage of the lyophilized control material up to 16 months compared to t = 0 months at 2°C to 8°C, and this study is ongoing. Stability of reconstituted PreciControls was evaluated by measuring them in (b) (4) after storage at various conditions. The data provided and reviewed demonstrate acceptable performance of controls upon storage for 5 hours at 20°C to 25°C after reconstitution, up to (b) (4) days at 2°C to 8°C, up to (b) (4) at (b) (4), and up to (b) (4). In-use stability data were acceptable for up to (b) (4) quality control procedures.

r) Within-Assay Carryover

Sample to sample carryover was evaluated using a panel of (b) (4) positive and (b) (4) negative samples run (b) (4) times on (b) (4) **cobas e** 801 analyzers. (b) (4) assay was used as a surrogate because (b) (4) could be generated. Every negative sample was exposed to potential carryover (b) (4) times. After sample processing, all negative samples were retested and yielded concentrations below the (b) (4) assay (b) (4). No sample-to-sample carryover was detected.

s) Cadaveric Studies

No cadaveric claims were sought by sponsor in this BLA.

t) Microbial Challenge

The analytical methods and their validations and/or qualifications reviewed for the Elecsys HTLV-I/II kit were found to be adequate for their intended use.

6. Clinical Studies

Clinical studies were conducted to evaluate assay sensitivity, specificity, and reproducibility to demonstrate performance in the intended use population of the

Elecsys HTLV-I/II assay. Testing was performed at three blood donor collection laboratories and confirmatory testing was conducted at one additional site. Three lots of the Elecsys HTLV-I/II Reagent Kit, and one lot each of the PreciControl HTLV, and the PreciControl HTLV Release Control Kit were used for the studies at each of the testing sites.

a) Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Elecsys HTLV I/II assay on the **cobas e** 801 analyzer and using an FDA licensed comparator assay by testing a total of 7677 specimens. All donors enrolled were evaluated and no donation was excluded.

Of the 7677 specimens tested, 3775 fresh serum and 3902 fresh plasma samples from voluntary blood donors were tested at three CTS sites using an FDA-licensed comparator HTLV assay. The specimens were collected from 6795 repeat donors and 882 first time donors. The initial and repeat reactive rate for the Elecsys HTLV I/II assay was 0.13% (10/7677, 7 serum and 3 plasma samples). Supplemental testing using an FDA-licensed assays revealed that 6 samples were non-reactive and 4 were inconclusive, followed by an expert panel resolution of inconclusive samples as non-reactive, confirming that the 10 Elecsys HTLV-I/II repeat reactive samples were false positive results. All 10 false positive results were obtained from repeat whole blood donors.

The specificity of the Elecsys HTLV-I/II assay relative to the final anti-HTLV antibody status in whole blood donors was calculated to be 99.87% (7667/7677) with a 95% Confidence Interval (CI) of 99.76% to 99.93%.

Table 5: Elecsys HTLV-I/II Clinical Study. Specificity of the Elecsys HTLV-I/II Assay in Donors

Specimen Category	N	IR (% of Total)	RR (% of Total)	Number Positive by Supplemental Testing (% of RR)	Specificity (%)[a] (95% CI)
Volunteer Blood Donors – Serum	3775	7 (0.19)	7 (0.19)	0 (0.00)	99.81 (3768/3775) (99.62 – 99.91)
Volunteer Blood Donors – Plasma	3902	3 (0.08)	3 (0.08)	0 (0.00)	99.92 (3899/3902) (99.77 – 99.97)
Total Volunteer Blood Donors	7677	10 (0.13)	10 (0.13)	0 (0.00)	99.87 (7667/7677) (99.76 – 99.93)

N = Number tested; IR = initially reactive; RR = repeatedly reactive; CI = confidence interval.
[a] Based on supplemental test results for the 10 repeatedly reactive specimens (7 serum and 3 plasma).

b) Clinical Sensitivity

Elecsys HTLV-I/II assay sensitivity was established by analyzing test results for 542 specimens that were identified as HTLV-positive. Testing was performed at three clinical sites. Elecsys HTLV-I/II repeatedly reactive specimens were confirmed with supplemental testing using an FDA-approved assay.
Of 542 tested specimens, 261 were HTLV-I positive, 243 were HTLV-II positive, and 38 were HTLV-undifferentiated positive.
Overall sensitivity was determined to be 100% (1977/1977) with a 95% confidence interval of 99.81% to 100% as presented in Table 6.

Table 6: Elecsys HTLV-I/II Clinical Study. Overall Sensitivity Summary

Specimen Category	N	Number Positive	Number RR (% of RR)	Number Positive by Supplemental Testing (% of RR)	Sensitivity (%) (95% CI)
Samples known to be positive for antibodies to HTLV-I	261	261	261 (100)	261 (100)	100 (98.55 – 100.00)
Samples known to be positive for antibodies to HTLV-II	243	243	243 (100)	243 (100)	100 (98.44 – 100.00)
HTLV Undifferentiated	38	38	38 (100)	38 (100)	100 (90.82 – 100.00)
Total	542	542	542 (100)	542 (100)	100 (99.30 – 100.00)

N = number tested; RR = Repeatedly Reactive.

c) Reactivity in Increased Risk Populations and Endemic Areas

Elecsys HTLV-I/II performance in an untested increased risk population and individuals from endemic areas was evaluated using a total of 1211 specimens. There were 1202 specimens non-reactive by Elecsys HTLV-I/II with a specimen status of negative and 9 samples repeatedly reactive by Elecsys HTLV-I/II assay. In the repeatedly reactive group 1 specimen was confirmed to be negative and 1 specimen had a status of inconclusive. Table 7 below summarizes the study data. Due to a small number of positive specimens, the sensitivity calculation was not performed.

Table 7. Elecsys HTLV-I/II Testing in Increased Risk Cohorts and Endemic Areas

Specimen Category	N	Number Initially Reactive (% of total)	Number Repeatedly Reactive (% of Total)	Number Positive by Algorithm Testing (% of RR)
Individuals at Increased Risk for HTLV-I/II Infection	409	9 (2.20)	9 (2.20)	7 (77.78)
Individuals from HTLV-I/II Endemic Areas	802	0	0	0
Total	1211	9 (0.74)	9 (0.74)	(0.74)

d) Reproducibility Studies

Reproducibility of the Elecsys HTLV-I/II assay was evaluated at three sites with (b) (4) instrument per site using three lots each of the Elecsys HTLV-I/II assay and one lot each of PreciControl HTLV as per CLSI EP05-A3. The panels were tested in random access mode for five days in two runs per day with three replicates per run using three lots of the Elecsys HTLV-I/II kits yielding 270 test results per panel member (5 days × 2 runs/day x 3 replicates × 3 reagent lots × 3 sites). The member panel included:

- (b) (4) low HTLV-I antibody sample at the target COI (b) (4)
- (b) (4) low HTLV-II antibody sample at the target COI (b) (4)
- (b) (4) high HTLV-I antibody sample at target COI (b) (4)
- (b) (4) high HTLV-II antibody sample at target COI (b) (4)

Additionally, three lots of PreciControls were tested as samples:

- PreciControl HTLV0 at target level COI (b) (4)
- PreciControl HTLV1 at COI (b) (4)
- PreciControl HTLV2 at target COI (b) (4)

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys HTLV-I/II assay. The results of the reproducibility panel and control testing demonstrate that the Elecsys HTLV-I/II assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 8.

Table 8: Overall Repeatability and Reproducibility for Elecsys HTLV-I/II

Sample	Mean COI	N	Repeatability		Between-Run		Between-Day		Within-Lab Within-Lot		Between-Site		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 16	1.97	270	0.031	1.55	0.017	0.872	0.016	0.806	0.039	1.95	0.000	0.000	0.074	3.73	0.083	4.21
HSP 17	9.73	270	0.144	1.48	0.103	1.06	0.020	0.203	0.178	1.83	0.024	0.249	0.623	6.41	0.649	6.68
HSP 18	1.92	270	0.028	1.44	0.025	1.32	0.005	0.251	0.038	1.97	0.000	0.000	0.058	3.04	0.070	3.62
HSP 19	11.8	270	0.187	1.58	0.133	1.12	0.065	0.550	0.239	2.02	0.038	0.325	0.299	2.53	0.385	3.25
*PC HTLV0	0.110	270	0.001	1.30	0.001	0.493	0.000	0.000	0.002	1.39	0.002	1.53	0.014	120.6	0.014	12.8
*PC HTLV1	5.07	270	0.090	1.78	0.083	1.63	0.000	0.000	0.122	2.41	0.000	0.000	0.276	5.45	0.303	5.98
*PC HTLV2	2.44	270	0.034	1.40	0.057	2.34	0.000	0.000	0.066	2.72	0.000	0.000	0.092	3.79	0.115	4.72
**PC HTLV0	0.110	270	0.002	1.45	0.000	0.000	0.001	0.506	0.002	1.54	0.002	1.38	0.014	12.7	0.014	12.8
**PC HTLV1	5.35	270	0.077	1.45	0.096	1.80	0.019	0.359	0.125	2.33	0.000	0.000	0.277	5.17	0.304	5.68
**PC HTLV2	2.83	269	0.054	1.89	0.043	1.52	0.013	0.468	0.070	2.47	0.000	0.000	0.103	3.63	0.125	4 43
***PC HTLV0	0.143	270	0.002	1.39	0.004	3.06	0.009	6.44	0.010	7.26	0.004	2.67	0.004	2.53	0.013	9.39
***PC HTLV1	4.97	270	0.087	1.76	0.057	1.14	0.005	0.096	0.104	2.09	0.000	0.000	0.260	5.22	0.280	5.63
***PC HTLV2	2.75	270	0.055	1.99	0.039	1.42	0.013	0.464	0.068	2.49 B	0.000	0.000	0.094	3.42	0.116	4.23

HSP=Human Specimens; PC= PreciControls; N = number of replicates; CV = coefficient of variation expressed as a percentage ((CVs are not meaningful when S/CO approaches zero); SD = standard deviation
Three lots of PreciControls were tested as samples; lots 1-3 are labeled with asterix

e) BIMO – Clinical/Statistical/Pharmacovigilance

A BIMO inspection assignment was issued for one domestic site participating in the study conduct of Protocol RD005615 in support of this BLA. The inspections did not reveal significant problems impacting the data submitted in the application.

f) Pediatrics

N/A

g) Other Special Populations

N/A

7. Advisory Committee Meeting

N/A

Summary Basis for Regulatory Action

8. Other Relevant Regulatory Issues

N/A

9. Labeling

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed instructions for use, package, and container labels on and found them acceptable from a promotional and comprehension perspective.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Review Committee reviewed the original submission and related Amendments. All review issues have been resolved; therefore, the Review Committee recommends licensure of the Elecsys HTLV-I/II assay.

b) Risk/Benefit Assessment

The risk/benefit analysis demonstrates that the benefit of the Elecsys HTLV-I/II assay outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 99.30 – 100.00), indicating a low probability of a false negative result. Among 7677 blood donors tested with the Elecsys HTLV-I/II assay, the assay specificity of 99.87% (95% CI of 99.76 – 99.93%) in clinical trials suggests a low probability of a false positive result.

c) Recommendation for Postmarketing Activities

No postmarketing activities have been proposed for this application.