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Summary Basis for Regulatory Action

Date: June 12, 2023

From: Rana Nagarkatti, Chair of the Review Committee

BLA/ STN#: 125778

Applicant Name: Roche Diagnostics

Date of Submission: August 16, 2022

MDUFA Goal Date: June 16, 2023

Proprietary Name: Elecsys HIV Duo

Established Name (common or usual name): Elecsys HIV Duo

Intended Use/Indications for Use:

Elecsys HIV Duo is an in vitro immunoassay for the simultaneous qualitative detection and differentiation of HIV-1 p24 antigen and antibodies to HIV, HIV-1 (groups M and O), and HIV-2 in human serum and plasma. Elecsys HIV Duo is intended to screen individual human donors, including volunteer donors of whole blood, blood components and source plasma. 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**mmuno**a**ssay "ECLIA" is intended for use with the **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: Nicole Verdun, 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.**

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(s) (product office) • *Clinical* • *Non-Clinical*	Ragupathy Viswanathan Virginie Dujols Mohan Kumar Haleyurgirisetty Iwona Fijalkowska	May 2, 2023 May 15, 2023 May 8, 2023 May 16, 2023
Statistical Review(s) • *Clinical* • *Non-Clinical*	Paul Hshieh	March 9, 2023
CMC Review • *CMC (Product Office)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DBSQC)* • *Establishment Inspection Report(s) (OCBQ/DMPQ)*	Krishnakumar Devadas Nitin Verma Alifiya Ghadiali Claire H. Wernly Alifiya Ghadiali	May 5, 2023 May 9, 2023 June 9, 2023 June 6, 2023 June 6, 2023
Labeling Review(s) • *Product Office* • *APLB (OCBQ/APLB)*	Rana Nagarkatti Sadhna Khatri	June 5, 2023 March 13, 2023
Lot Release Protocols/Testing Plans	Ishrat Sultana Varsha Garnepudi	June 6, 2023 June 9, 2023
Bioresearch Monitoring Review	Haecin Chun	May 4, 2023
Software and Instrumentation	Hongqiang Hu	May 24, 2023
Tissues and Advanced Therapies (OTAT)	Hanh Khuu	May 1, 2023

1. Introduction

The Elecsys HIV Duo assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4), Germany. This biologics license application (BLA) for Elecsys HIV Duo assay from Roche Diagnostics Solutions, 9115 Hague Road Indianapolis, IN 46250, USA was received on August 16, 2022.

The Roche Elecsys HIV Duo (BP190403) modular PMA was approved by FDA on April 10, 2020, for aid in the diagnosis for HIV-1 and HIV-2 infection in human serum and plasma. The Elecsys HIV Duo assay (b) (4) under review for donor screening utilizes the same assay technology, reagents, assay controls, general purpose reagents, and result generation software sub-routines, as the approved Elecsys HIV Duo assay for diagnosis (BP190403) to detect and

differentiate HIV-1 p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in human serum and plasma. The BLA was preceded by investigational new drug application (IND) 27257 received on January 19, 2021. An overview of the cobas pro Serology Solutions, cobas e 801 instrumentation, and software, reviewed in BP090403 is summarized in this original BLA submission.

Due to commonalities between the technology and assay formats for the Elecsys assays and the use of the cobas e 801 analyzer and cobas pro serology solution for donor screening, Roche was advised to submit one IND for the Elecsys HIV Duo, Elecsys Anti-HCV II, Elecsys HBsAg II, Elecsys HBsAg II Auto Confirm, Elecsys Anti-HBc II, Elecsys HTLV-I/II, Elecsys Chagas, Elecsys Syphilis, and Elecsys CMV IgG assays. Thirteen amendments to the IND were received. The last amendment was received on December 21, 2022. Pre-submission discussions were conducted with Roche on regulatory aspects related to software and instrumentation, pre-clinical studies, and clinical studies, for all Elecsys assays in the bundled IND (BQ170139/0, telecon held March 15, 2018; BQ170139/1, telecon held September 17, 2020; BQ170139/2, telecon held October 7, 2020; BQ170139/3, written response provided February 26, 2021; BQ170139/3.

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

Date	Action	Amendment to BL125778
August 16, 2022	BLA CBER receipt	
August 17, 2022	Acknowledgement Letter	
August 26, 2022	Revised FDA-356h submitted by RD	/0/1
September 28, 2022	Filing Notification Letter	
October 3, 2022	FDA IR- DMPQ (CMC comparison between BLA and BP170139)	
October 17, 2022	Sponsor response to IR	/0/2
November 1, 2022	FDA IR – Clinical (clinical data issues)	
November 15, 2022	Sponsor response to IR	/0/3
November 10, 2022	FDA site requirement telecon with RD	
November 18, 2022	Meeting minutes of site requirement telecon	/0/4
January 19, 2023	FDA IR – Request for Lot Release Template	
January 20, 2023	FDA IR – Bioburden and (b) (4) methods	
January 30, 2023	FDA IR – Clarification for installation of cobas e 801 at CBER. A consolidated IR comments and draft-Package Insert	

Summary Basis for Regulatory Action

Date	Action	Amendment to BL125778
January 31, 2023	FDA IR – Validation Lot Summary and deviations	
February 2, 2023	Lot Release Template submitted by RD	/0/5
February 6, 2023	Response to FDA IR for system installation at CBER	/0/6
February 21, 2023	Response to FDA consolidated IR	/0/7
March 3, 2023	Response to FDA IR for validation lot summary and deviations	/0/8
March 3, 2023	Response to FDA IR for Bioburden and (b) (4) methods	/0/9
March 10, 2023	Correction to (b) (4) report submitted by RD	/0/10
March 31, 2023	FDA IR - Additional request for Bioburden and (b) (4) methods	
April 14, 2023	Response to FDA IR for additional information on Bioburden and (b) (4)	/0/11
April 14, 2023	Telecon with RD to discuss Lot Release Protocol (LRP) template	
April 24, 2023	RD submitted restructured LRP template	/0/12
May 3, 2023	Telecon with RD to discuss bioburden testing	
May 8, 2023	Amendment received for updating the serology controller software from version 1.0.3 to version 1.1	/0/13
May 8, 2023	RD corrected of STN number for software update amendment	/0/14
May 12, 2023	Amendment received with additional verification data for Bioburden testing	/0/15
May 12, 2023	RD submitted meeting minutes for May 3 telecon	/0/16
May 18, 2023	RD submitted corrected FDA form 356h due to incorrect site information	/0/17
May 24, 2023	RD submitted additional verification data for Bioburden testing	/0/18
May 24, 2023	FDA IR- Requested RD to provide final LRP template, conformance lot testing data and bioburden protocol	
May 25, 2023	Response to FDA IR- RD submitted response with additional information on bioburden testing methods and LRP template.	/0/19
May 26, 2023	Response to FDA IR- RD submitted final LRP Template	/0/20

Date	Action	Amendment to BL125778
May 31, 2023	Response to FDA IR- RD submitted signed LRP template with test results generated using (b) (4) blinded panels with (b) (4) conformance lots	/0/21
June 1, 2023	FDA IR- Draft PI with comments communicated to RD	
June 12, 2023	Response to FDA IR-RD submitted the final PIs	/0/22

2. Background

The Elecsys HIV Duo assay is a qualitative serologic sandwich immunoassay intended for the detection and differentiation of HIV-1 p24 antigen and antibodies to HIV-1, HIV-1(group M, and group O) and HIV-2, in human serum and plasma. This assay design consists of two modules, one for detection of HIV-1 p24 antigen using monoclonal antibodies to (HIV-1) p24 and the second module for the detection of HIV-1 and HIV-2 antibodies using recombinant antigens derived from the Env and Pol-region of HIV-1 (including group O) and HIV-2. Additional controls, calibrators and general use reagents are also required to perform the assay and described in the CMC section below. The immunoassay is based on the electrochemiluminescence immunoassay (ECLIA) principle. 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. This assay utilizes the two e-flow software modules, HIVDUOB for initial test result and HIVDUOBR for repeat test result calculations. Assay results are calculated using measurements obtained from both the HIVAGB, and the AHIVB modules, and their respective assay calibrators (used to establish a module and kit-lot specific cut-off index (COI, the term used interchangeably with S/CO). The main result for the Elecsys HIV Duo assay is calculated using the sub-results for each module as follows:

$$\text{HIVDUO (COI)} = \sqrt{(\text{HIVAGB [COI]})^2 + (\text{AHIVB [COI]})^2}$$

The assay results are reported as a reactive (R) or repeat reactive (RR) for COI ≥ 1.00 and non-reactive (NR) for COI < 1.00.

3. Chemistry Manufacturing and Controls (CMC)

The manufacture of the Elecsys HIV Duo assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

Summary Basis for Regulatory Action

The Elecsys HIV Duo assay is manufactured at the Roche Diagnostics GmbH facilities in Germany located at (b) (4)
Sandhofer Strasse 116, Mannheim, 68305, Germany.
Elecsys HIV Duo assay kit (List Number 08836973162, 300 tests) consists of two modules, one bundled reagent pack (cobas e pack) for HIV Ag (HIV-1 p24 antigen) detection, referred to as HIVAGB, and the second bundled cobas e pack for Anti-HIV (HIV-1 and HIV-2 antibody) detection, referred to AHIVB.

The Elecsys HIV Duo HIVAGB (Module M1, HIV Antigen) includes ten reagent cassettes for HIV-1 p24 antigen detection and consists of the following components:

- Component M: Streptavidin-coated microparticles for capturing biotin complex.
- Components R1 and R2: Biotinylated/ ruthenylated monoclonal anti-HIV-1 p24 antibodies.
- HIVDUO Cal1: Negative human serum (human serum, negative for HBsAg, anti-HCV and anti-HIV1/2 antibodies, non-reactive for HIV-1 RNA and HCV-RNA).
- HIVDUO Cal2: Recombinant HIV-1 p24 antigen in negative human serum.

The Elecsys HIV Duo AHIVB (Module M2, anti-HIV) includes ten reagent cassettes for anti-HIV (HIV-1 and HIV-2 antibody) detection and consists of the following components:

- Component M: Streptavidin-coated microparticles for capturing biotin complex.
- Components R1 and R2: Biotinylated/ ruthenylated recombinant HIV-1 (b) (4) antigen, synthetic HIV-1 (b) (4) peptides and synthetic HIV-2 (b) (4) peptides, recombinant HIV-1 (b) (4) antigen and recombinant HIV-2 (b) (4) antigen.
- HIVDUO Cal3: Negative human serum (human serum, negative for HBsAg, anti-HCV and anti-HIV1/2 antibodies, non-reactive for HIV-1 RNA and HCV-RNA).
- HIVDUO Cal4: Human serum reactive for anti-HIV-1 antibodies.

PreciControl HIV Gen II (List Number 06924107162) and PreciControl HIV, HIV-2+GrpO (List Number 06924115162), supplied separately, are used for quality control of Elecsys HIV Duo and consists of the following components:

- PC HIV1B Gen II: Human serum, negative for HBsAg, anti-HCV and anti-HIV1/2 antibodies and non-reactive for HIV-1 RNA and HCV-RNA.
- PC HIV2B Gen II: Human serum positive for anti-HIV-1 antibodies.
- PC HIV3B Gen II: Recombinant HIV-1 p24 antigen.
- PC HIV4B Gen II: Human serum positive for anti-HIV-2 antibodies.
- PC HIV5B Gen II: Mouse anti-HIV-1 Group O monoclonal antibodies.

PreciControl Release HIV Gen II (List Number 09367101190) is used as a Release Control, supplied separately, is identical to PC HIV2B Gen II, and consists of the following component:

- PC HIVR: Human serum positive for anti-HIV-1 antibodies.

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

- ProCell II M (List Number 06908799190): System reagent for generating electrochemical signal.
- CleanCell M (List Number 04880293190): Cleaning solution for the measuring cell.
- Reservoir cup (List Number 07485409001): Cups to supply ProCell II M and CleanCell M solutions.
- PreClean II M (List Number 06908853190): Wash solution.
- Elecsys SysClean (11298500316): System cleaning solution.
- AssayTip/AssayCup tray (List Number 05694302001): Disposable pipetting tips and reaction vessels.
- Liquid Flow Cleaning Cup (List Number 07485425001): Cups to supply ISE Cleaning Solution/Elecsys SysClean.
- PreWash Liquid Flow Cleaning Cup (List Number 07485433001): Cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit.
- ISE Cleaning Solution/Elecsys SysClean (List Number 11298500160): ISE Cleaning Solution/Elecsys SysClean system cleaning solution.

b) Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the Elecsys HIV Duo kit were 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

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 the facility involved in the manufacture of Elecsys HIV Duo are summarized in the table below (Table 3).

Summary Basis for Regulatory Action

Table 3: Manufacturing Facility for Elecsys HIV Duo

Manufacturing / Testing Activities	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
Roche Diagnostics GmbH (b) (4) Germany *Manufacturing of Elecsys kit components and Control reagents Release testing of final device (assay)*	(b) (4)		Waiver	CDER Pre-License Inspection (b) (4) VAI ORA Post-Market Approval Inspection (b) (4) NAI
Roche Diagnostics GmbH Sandhofer Str. 116, 68305 Mannheim, Germany *Labeling and packaging (Elecsys kit assembly), manufacturing, labeling and packaging of system reagents*	3002806559	315028860	Waiver	MRA Inspection Review by ORA/OPQO (b) (4) ; VAI ORA For-Cause Inspection (b) (4) VAI ORA Post-Market Approval Inspection (b) (4) 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) , Germany

The Center for Drug Evaluation and Research conducted a pre-license inspection at Roche Diagnostics GmbH, (b) (4) , Germany (b) (4) The inspection covered 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).

ORA performed a post-market approval inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) The inspection covered Elecsys assay kits. No FDA Form-483 was issued, and the inspection was classified as No Action Indicated (NAI).

An additional inspection, a MRA inspection review and a records request were performed between (b) (4) for drug substance and drug product regulated by CDER and were classified as either VAI or NAI.

Roche Diagnostics GmbH, Mannheim, Germany

The Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations performed a review of a foreign surveillance inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) under the Mutual Recognition Agreement. The firm's responses to the deviations identified were found acceptable. A GMP certificate is available in the European Union Drug Regulatory Authorities Network database. Based on review of the report, this inspection was classified by ORA as VAI.

ORA performed a for-cause inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) . All FDA Form-483 issues were resolved, and the inspection was classified as VAI.

ORA performed a post-market approval inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) . No FDA Form-483 was issued and the inspection was classified as No Action Indicated.

One additional inspection was performed in (b) (4) for a drug product regulated by CDER and 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 pro serology solution User Guide version 1.5.

b) Device Description

The cobas pro serology solution is a combination of the cobas pro serology controller (software), cobas pro integrated solutions (with 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 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 parameters 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 pro 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 HIV Duo test results) and 10 are related to a use of 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 HIV Duo 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 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.

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 Elecsys HIV Duo BLA are not impacted by this update.

5. Analytical Studies

Elecsys HIV Duo was approved for diagnostic use in PMA BP190403. As agreed, in Q-Submission BQ170139/Supplement 3, the analytical data submitted, reviewed, and approved in the PMA BP190403, sufficiently demonstrated the analytical performance of Elecsys HIV Duo assay reagent packs, PreciControl HIV Gen II and PreciControl HIV; HIV-2+GrpO for use in donor screening. Data previously submitted are summarized below. Additionally, new and amended study data were submitted by Roche to support claims in the package insert.

Non-clinical studies were performed at Roche Diagnostics GmbH, (b) (4) to evaluate the performance of the Elecsys HIV Duo assay. The analytical studies were conducted in compliance with 21 CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

a) Limit of Detection

(b) (4)

(b) (4)

b) Seroconversion Sensitivity

The seroconversion sensitivity of the Elecsys HIV Duo assay was compared to the sensitivity of an FDA-approved assay. Three lots of the Elecsys HIV Duo were used to test a total of 50 seroconversion panels. There were no panel members with discordant results between the Elecsys HIV Duo assay and the comparator assay. For 47 of the 50 panels, the first reactive time point for the Elecsys HIV Duo assay occurred at the same time as the first reactive time point for the comparator assay. For two panels, the Elecsys HIV Duo assay demonstrated earlier detection by 2 and 3 days compared to the comparator assay. One bleed specimen was not tested by the comparator assay but tested reactive with the Elecsys HIV Duo assay.

Review Note: For 10 of the 50 panels that were (b) (4), the first reactive time point remained the same compared to the seroconversion data submitted in PMA BP190403. There were no discrepant results with respect to antigen and antibody reactivity, or the time to first reactive test result, for the panels tested in both the PMA and the BLA.

c) Endogenous Interferences (Spiked)

Assay performance was evaluated in samples with high levels of spiked interferants (hemoglobin, lipemia, bilirubin, and human serum albumin for total protein) using matched sets of serum and plasma donor specimens of all specified types: (b) (4) The data provided and reviewed demonstrate acceptable performance of the assay for both nonreactive and reactive samples, supporting the use of donor specimens containing up to 500 mg/dL of hemoglobin, up to 2000 mg/dL lipid, up to (b) (4) mg/dL bilirubin, and up to (b) (4) g/dL of total protein in the Elecsys HIV Duo assay. In addition, (b) (4) No interference was observed up to 1200 ng/mL of biotin using the Elecsys HIV Duo assay.

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. A total of (b) (4) specimens for each interferent were used. No false reactive results were obtained. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of specimens that contain up to (b) (4) of hemoglobin (range tested (b) (4)

(b) (4) up to (b) (4) of triglycerides (range tested (b) (4) , up to (b) (4) of total bilirubin (range tested (b) (4) up to (b) (4) of total protein (range tested (b) (4) and up to (b) (4) rheumatoid factor (range tested (b) (4)

e) Analytical Sensitivity

The analytical sensitivity of the Elecsys HIV Duo assay was evaluated using the WHO 1st International Standard for HIV-1 p24 antigen (NIBSC Code 90/636), diluted to target concentrations between (b) (4) IU/mL. Seven dilutions of each standard were prepared and measured. (b) (4) were evaluated to determine Elecsys HIV Duo antigen sensitivity in pg/mL. Three lots of Elecsys HIV Duo assay were used for measurements on one cobas e 801 analyzer. Analytical sensitivity was calculated from the S/CO and corresponding antigen standard dilutions tested. The mean results from three kit lots demonstrated antigen sensitivity of (b) (4) IU/mL using the NIBSC standard, (b) (4) .

f) Group, Subtype and Circulating Recombinant Form (CRF) Detection

Assay performance was tested with (b) (4) viral lysates for the detection of HIV-1 p24 antigen using HIV-1/(b) (4) (n = (b) (4), and (b) (4) of (b) (4) , HIV-1/N (n = (b) (4), HIV-1/ (b) (4) (n= (b) (4), (b) (4) HIV1/P, and (b) (4) , and (b) (4) (n = (b) (4)) reactive samples. Assay performance was also tested with serum and plasma samples for the detection of HIV antibodies and included HIV-1/(b) (4) (n = (b) (4), and (b) (4) of (b) (4) , HIV-1/ (b) (4) (n= (b) (4), (b) (4) of HIV-1/N and HIV-1/P, and (b) (4) reactive samples. All 58 samples tested reactive with the Elecsys HIV Duo assay.

g) Cross Reaction/Analytical Specificity

Assay performance when used to test specimens with other conditions or disease states (n = 100) unrelated to HIV infection was evaluated. Testing was conducted with neat specimens and aliquots individually spiked with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody.

The effect of potentially interfering factors was tested with the Elecsys HIV Duo assay with specimens:

- containing antibodies against HAV, HBV, HCV, HTLV- I/II, CMV, EBV, HSV 1/2, (b) (4) Rubella, Rotavirus, Smallpox, VZV
- containing autoantibodies (ANA) and elevated titers of rheumatoid factor
- positive for antibodies against Candida, E. coli, Plasmodium falciparum/vivax, Mycobacterium tuberculosis, Chlamydia, Treponema pallidum (syphilis)
- after vaccination against HAV, HBV, and influenza
- from patients with monoclonal gammopathy and multiple myeloma/ lymphoma, common cold, Graves' disease, Crohn's disease

- from pregnant women 1st, 2nd and 3rd trimester, multiparous pregnancies

The data provided and reviewed demonstrate acceptable performance of the assay as the presence of potentially interfering substances or medical conditions had no effect on the detection of HIV-1 or HIV-2 antibodies or HIV-1 antigen. There was no significant effect on background signals in negative specimens (neat specimens).

Review Note: Cross-reactivity data with potential interfering agents, with (b) (4) spiked samples, were reviewed and found acceptable in PMA BP190403. A subset of these spiked samples was retested with the updated Elecsys HIV Duo assay (containing scavenger antibodies for biotin) to demonstrate equivalence with the original assay.

h) Hook Effect

Assay performance was evaluated using (b) (4) for HIV-1 p24 antigen (n= (b) (4) highest S/CO = (b) (4)), and high titer specimens for HIV-1 antibody (n= (b) (4) highest S/CO = (b) (4)), HIV-1 GrpO antibody (n= (b) (4) S/CO = (b) (4)), and HIV-2 antibody (n= (b) (4) highest S/CO = (b) (4) diluted in negative serum in (b) (4) dilution steps to produce a dilution series yielding a range of S/CO values from negative to high positive values. The data provided and reviewed demonstrate acceptable performance of the assay as all high titer specimens tested reactive. No false negative results were obtained due to hook effect.

i) Serum and Plasma Comparison

Assay performance when used to test blood specimens collected from individual donors in tubes containing Lithium heparin, Sodium heparin, Sodium citrate, di-Potassium EDTA, tri-Potassium EDTA, ACD, CPD, CPDA, CP2D, and Potassium Oxalate (plasma preparation tubes), lithium heparin (plasma separator tubes), and serum gel separation tubes, were compared to performance when used to test specimens collected in serum tubes. Additionally, the suitability of serum and plasma from Li-Heparin primary specimen tubes with separating gel was tested by comparing them to Li-Heparin tubes without separating gel. The impact of anticoagulants on the performance of the Elecsys Duo assay was evaluated using matched sets of serum and plasma specimens of all specified types, HIV negative (n=50) or spiked with HIV-1 p24 antigen (n=40), HIV-1 antibody (n=40), and HIV-2 antibody (n=10). The samples were spiked to a target concentration of ranging from (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay with specimens collected in various anticoagulants and tube types supporting the use of specimens collected in all tube types listed above.

j) Specimen Storage

Assay performance when used to test serum and plasma specimens stored at various temperatures was evaluated using (b) (4) serum and (b) (4) plasma specimens – HIV negative (n= (b) (4) or spiked with HIV- (b) (4) antigen (n= (b) (4) HIV- (b) (4) antibody (n= (b) (4) and HIV- (b) (4) antibody (n= (b) (4) and (b) (4) – compared to specimens 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 serum and plasma specimens that were stored at approximately 15 to 25°C for up to 7 days, 2 to 8°C for up to (b) (4) weeks, -20°C or colder for up to (b) (4) months, and up to (b) (4) freeze/thaw cycles.

k) Specimen Processing

Assay performance when used to test centrifuged non-frozen and previously frozen specimens was evaluated using (b) (4) serum specimens – HIV negative (n=(b) (4) or spiked with HIV-(b) (4) antigen (n=(b) (4), HIV(b) (4) antibody (n=(b) (4), HIV-(b) (4) antibody (n =(b) (4), and HIV(b) (4) antibody (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 with non-frozen and previously frozen serum specimens for 10 to 15 minutes at 2000 to 4000 RCF (relative centrifugal force = x g).

l) On-clot Specimen Processing

Assay performance when used to test 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 – HIV negative (n=(b) (4) or spiked with HIV-(b) (4) antigen (n=(b) (4), HIV(b) (4) antibody (n=(b) (4), and HIV(b) (4) antibody (n=(b) (4)) – 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 with samples stored on-clot for 7 days at 15 to 30°C and 14 days at 2 to 8°C.

Review Issue: Roche utilized an assay acceptance criteria for the on-clot stability study that positive specimens remain positive and negative specimens remain negative after storage on-clot. This acceptance criterion was broad and not utilized for other stability studies. Applying an acceptance criterion for other stability studies of an average recovery of HIV negative to be within (b) (4) S/CO and HIV positive specimens to be within (b) (4) (S/CO) resulted in one low positive HIV p24 sample failing on-clot stability with a recovery of (b) (4). In BQ 170139/3, Roche presented broad and variable acceptance criteria for several analytical studies (ranging from (b) (4) (S/CO) for some studies while for other studies it was (b) (4) deviation from S/CO). To be consistent across analytical studies in BQ 170139/3 FDA recommended a ± 20% deviation of S/CO in target positive specimens/samples used for stability studies across all Elecsys donor screening assays. Based on this recommendation the on-clot stability a recovery of (b) (4) was acceptable to the review team.

m) Kit Lot Calibration and On-Board Calibration Stability

Calibration of the Elecsys HIV Duo assay must be performed once per reagent lot using HIVDUO Cal1 and HIV DUO Cal2 for (b) (4), and HIVDUO Cal3 and HIV DUO Cal4 for (b) (4). Lot calibration stability was validated using Elecsys HIV Duo 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, – HIV negative (n=(b) (4) or spiked at a minimum of

(b) (4) reactivity levels (b) (4) with HIV-(b) (4) antigen (n=(b) (4), HIV-(b) (4) antibody (n=(b) (4), HIV-(b) (4) antibody (n=(b) (4), HIV(b) (4) antibody (n=(b) (4), and a serum specimen positive for both HIV-(b) (4) antigen and HIV(b) (4) antibody with and without (b) (4), 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 was utilized to test stability of the Elecsys HIV Duo kit components stored on-board a cobas e 801 analyzer for (b) (4) 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 validated using (b) (4) Elecsys HIV Duo kit lots stored a 2 to 8°C up to (b) (4) months compared to t = 0 months. A total of (b) (4) serum specimens, HIV negative (n=(b) (4) or spiked with HIV-(b) (4) antigen (n=(b) (4), HIV(b) (4) antibody (n=(b) (4), HIV-(b) (4) antibody (n=(b) (4), and HIV(b) (4) antibody (n=(b) (4) at a minimum of (b) (4) reactivity levels (b) (4) along with (b) (4) 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 24 months. In addition, the same panel, with (b) (4) additional panel members – (b) (4) – was utilized to evaluate on-board stability of the Elecsys HIV Duo kit components when stored at 20 to 25°C for (b) (4) weeks and at (b) (4) for (b) (4) weeks to evaluate stability during shipping, and results compared to unstressed kits stored at 2 to 8°C. Acceptable performance was observed, supporting an on-board stability claim of up to 16 weeks and a transportation claim of up to (b) (4) weeks.

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

Assay performance when used to test specimens, calibrators, and controls directly after storage at 2 to 8°C was evaluated using (b) (4) serum specimens—HIV negative (n=(b) (4) or spiked at (b) (4) reactivity levels with HIV-(b) (4) antigen (n=(b) (4), HIV-(b) (4) antibody (n=(b) (4), HIV-(b) (4) antibody (n =(b) (4), and HIV-(b) (4) antibody (n=(b) (4) — compared to samples that were equilibrated at (b) (4) (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 (b) (4) minutes.

p) Calibrator Stability

Stability of calibrators was evaluated by reconstituting the (b) (4) HIVDUO calibrators and measuring them in (b) (4) storage at various conditions. The data provided and reviewed demonstrate acceptable performance of

calibrators supporting stability claims of storage at 20 to 25°C for 5 hours, at 2 to 8°C for up to 3 days, at (b) (4) for up to (b) (4) weeks, and up to (b) (4).

q) PreciControl Stability

Stability of PreciControl HIV Gen II and PreciControl HIV; HIV-2+GrpO was evaluated by reconstituting the (b) (4) PreciControls and measuring them in (b) (4) after storage at various conditions. The data provided and reviewed demonstrate acceptable performance of calibrators supporting stability claims of storage at 20 to 25°C for 5 hours, at 2 to 8°C for up to 7 days, at (b) (4) for up to (b) (4), and up to (b) (4). In-use stability data were acceptable for up to (b) (4) quality control procedures.

r) In-House Specificity (Donors)

The specificity of the Elecsys HIV Duo assay was determined by testing a minimum of (b) (4) unlinked serum and plasma specimens from blood donors using (b) (4) reagent kit lots. This was an internal investigational study carried out at Roche Diagnostics GmbH, (b) (4) Germany and the results summarized in the Clinical Specificity section below. The data were not utilized for calculating the clinical specificity of the assay.

s) 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.

Review Note: As agreed with the sponsor, in Q-Submission BQ170139/3, the analytical data submitted, reviewed, and approved in the PMA BP190403, sufficiently demonstrated the analytical performance of Elecsys HIV Duo for use in donor screening. Studies summarized in **b, f, g, k, l, m, n, o, r,** and **s** sections above contained new and/or amended data submitted for review in this BLA to support changes to the sample preparation, testing instructions, and stability claims documented in the package insert.

t) Cadaveric Studies

No cadaveric claims were sought by sponsor in this BLA.

Review Note: Roche stated that (b) (4)

u) Microbial Challenge

The analytical methods and their validations and/or qualifications reviewed for the Elecsys HIV Duo kit were found to be adequate for their intended use.

6. Clinical Studies

Clinical studies were conducted to evaluate assay specificity and reproducibility to demonstrate performance in the intended use population of the Elecsys HIV Duo assay. Testing was performed at four blood donor testing laboratories using specimens collected at four whole blood collection sites and one plasmapheresis collection site. Three lots of the Elecsys HIV Duo Reagent Kit, and one lot each of the Elecsys HIV Duo Calibrator Kit, the Elecsys HIV Duo Assay Control Kit, and the Elecsys HIV Duo Release Control Kit were used for the studies at testing sites.

a) Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Elecsys HIV Duo assay on the cobas e 801 analyzer using a total of 17,168 specimens collected at three whole blood donor collection centers and one source plasma collection center. All donors enrolled were evaluated and no donation was excluded.

Of the 17,168 specimens tested, 14,169 whole blood samples were tested: 11, 168 at three CTS sites using an FDA licensed comparator HIV-1/2 antibody assay and 3,001 at one (b) (4) site using an FDA licensed comparator HIV-1/2 antibody assay and an FDA licensed antigen/antibody combo assay. A total of 7,071 fresh serum and 7,098 fresh plasma from voluntary blood donors were tested and included 12,336 repeat donors and 1,833 first time donors. The initial and repeat reactive rate for the Elecsys HIV Duo assay was 0.098% (14/14,169, 6 serum and 8 plasma samples). Of the 14 Elecsys HIV Duo repeat reactive samples, seven were generated at the CTS testing sites, six of which were reactive on the AHIVB antibody detection module, and one was reactive on the HIVAGB antigen detection module. Of the remaining seven repeat reactive samples generated at (b) (4) testing site, five were reactive on the AHIVB antibody detection module, and two were reactive on the HIVAGB antigen detection module. Although the HIVAGB and AHIVB modules independently report NR, R, or RR results based on S/CO values, a single S/CO result is calculated and reported by the Elecsys HIV Duo assay HIVDUOB module and reported as R or NR. Final donor status is determined by the HIVDUOBR module utilized for repeat testing. Supplemental testing using an FDA-licensed antibody assay and NAT confirmed that 13 of the 14 Elecsys HIV Duo repeat reactive samples were false positive. The final result of one repeatedly reactive serum specimen was inconclusive due to a supplemental test system flag; however, this sample was non-reactive with comparator assay and NAT, and the final status was determined to be negative. All 14 false positive results were obtained from repeat whole blood donors. The specificity of the Elecsys HIV Duo assay relative to the final HIV status in whole blood donors was calculated to be 99.90% (14,155/14,169) with a 95% Confidence Interval (CI) of 99.83% to 99.95%.

Of the 17,168 specimens, 2,999 samples were from source plasma donors and were tested at one CTS site. None of the source plasma samples tested reactive with the Elecsys HIV Duo assay. The specificity of the Elecsys HIV Duo assay relative to the

final HIV status in source plasma was calculated to be 100% (2,999/2,999) with a 95% CI of 99.87% to 100.00%.

The overall specificity of all donations relative to the final HIV status of all donations (serum, plasma from voluntary blood donors, and source plasma donors) from CTS and (b) (4) combined testing sites is 99.92% (17,154/17,168) with a 95% CI of 99.86% to 99.95% (Table 4).

Table 4: Elecsys HIV Duo Clinical Study Reactivity of the Elecsys HIV Duo 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	7,071	6 (0.08)	6 (0.08)	0 (0.00)	99.92 (7,065/ 7,071) (99.81 – 99.96)
Volunteer Blood Donors – Plasma	7,098	8 (0.11)	8 (0.11)	0 (0.00)	99.89 (7,090 / 7,098) (99.78 – 99.94)
Total Volunteer Blood Donors	**14,169**	**14 (0.09)**	**14 (0.09)**	**0 (0.00)**	**99.90 (14,155 / 14,169) (99.83 – 99.95)**
Plasmapheresis Donors	**2,999**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**100 (2,999 / 2,999) (99.87 – 100.00)**
Overall Donors	**17,168**	**14 (0.08)**	**14* (0.08)**	**0 (0.00)**	**99.92 (17,154 / 17,168) (99.86 – 99.95)**

N = Number tested; IR = initially reactive; RR = repeatedly reactive; CI = confidence interval.
[a] Based on supplemental test results for the 14 repeatedly reactive specimens (6 serum and 8 plasma).
*One repeatedly reactive serum specimen was inconclusive due to a supplemental test system flag; however, this sample was non-reactive with comparator assay and NAT testing and final status determined to be HIV negative.

Review Note:
An FDA IND non-hold comment recommended that Roche test 1/3 of all donations using an FDA licensed antigen/antibody combo assay as comparator in addition to an FDA licensed HIV-1/2 antibody assay because the Elecsys HIV Duo test results are calculated using the HIVAGB antigen detection module in addition to the AHIV antibody detection module. Roche selected the (b) (4) site as it had already implemented donor screening with the FDA licensed antigen/antibody combo assay. Supplemental testing results for the seven Elecsys HIV Duo repeat reactive samples generated at (b) (4) indicated that all seven were false positives. The specificity of the Elecsys HIV Duo assay relative to the final HIV status at this site in whole blood donors was calculated to 99.77% (2,994/3,001) with a 95% CI of 99.52% to 99.91%. Because of the high false-positive rate at the (b) (4) site and to determine the poolability of results, Roche conducted an internal investigation with a new cohort of (b) (4) HIV negative blood donor

samples collected from (b) (4) and found (b) (4) repeat reactive. No sources of bias were identified, and the data was deemed poolable.

b) Clinical Sensitivity

As agreed in Q-Submission BQ170139/Supplement 3, the clinical sensitivity data submitted, reviewed, and approved in the PMA BP190403 sufficiently demonstrated the clinical sensitivity performance of Elecsys HIV Duo for use in donor screening. Data previously submitted in PMA BP190403 are summarized below and no new clinical sensitivity study was performed.

Assay sensitivity was calculated by analyzing test results for 1,977 specimens that were identified as HIV positive from 10, 121 total samples and used to establish the sensitivity of the Elecsys HIV Duo assay with testing performed at three clinical sites. Elecsys HIV Duo repeat reactive specimens were confirmed with supplemental testing using an FDA-approved antigen and antibody detection assay and/or a reactive using an FDA -approved HIV NAT. Overall sensitivity was estimated to be 100% (1977/1977) with a 95% confidence interval of 99.81% to 100% (Table 5).

Table 5: Elecsys HIV Duo Clinical Study Overall Sensitivity Summary

Specimen Category	N	Number Positive	Number RR (% of RR)	Number RR that were Positive by Supplemental Testing (% of RR)	Sensitivity (%) (95% CI)
All samples known to be positive for antibodies to HIV-1	1,409	1,409	1,409 (100)	1,409 (100)	100% (99.74 – 100.00)
All samples known to be positive for antibodies to HIV-2	200	200	200 (100)	200 (100)	100% (98.17 – 100.00)
HIV-1 antigen positive / antibody negative	52	52	52 (100)	52* (100)	100% (93.15 – 100.00)
HIV-1 (Group M subtypes)	90	90	90 (100)	90 (100)	100% (95.98 – 100.00)
HIV-1 Group O	50	50	50 (100)	50* (100)	100% (92.89 – 100.00)
Individuals at high risk of HIV-1/2 infection	1,410	162	168 (11.91)	162 (96.43)	100% (97.75 – 100.00)

Specimen Category	N	Number Positive	Number RR (% of RR)	Number RR that were Positive by Supplemental Testing (% of RR)	Sensitivity (%) (95% CI)
Individuals at low risk of HIV-1/2 infection	6,910	14	21 (0.30)	14 (66.66)	100% (76.84 – 100.00)
Total	**10,121**	**1,977**	**1,990 (19.66)**	**1,977 (99.34)**	**100% (99.81 – 100.00)**

N = number tested; RR = Repeatedly Reactive.
*One sample for this specimen category for repeat testing so the respective certificate of analysis was used to provide objective evidence of HIV infection.

c) Reproducibility Studies

Reproducibility of the Elecsys HIV Duo assay was evaluated at three sites with (b) (4) instrument per site using three lots each of the Elecsys HIV Duo assay and 1 lot each of PreciControl HIV Gen II, PreciControl HIV, HIV 2+GrpO and PreciControl Release HIV Gen II as per (b) (4) . The panels were tested in random access mode in two runs per day for five days with three replicates per run using three lots of the Elecsys HIV Duo kits yielding 270 test results per panel member (2 runs/day × 5 days × 3 replicates × 3 sites × 3 lots). The 12-member panel included:

- (b) (4) low HIV antibody panel members for HIV-1 Grp M, HIV-2, and HIV-1 GrpO with target S/CO (b) (4)
- (b) (4) low HIV-1 p24 antigen with target S/CO (b) (4)
- (b) (4) high HIV antibody panel members for HIV-1 Group M, and HIV-2 with target S/CO (b) (4)
- (b) (4) high HIV-1 p24 antigen with target S/CO (b) (4)
- PC HIV1 B, HIV negative with target S/CO approximately (b) (4)
- PC HIV2 B, HIV-1 antibody positive with target S/CO approximately (b) (4)
- PC HIV3 B, HIV p24 antigen positive with target S/CO approximately (b) (4)
- PC HIV4 B, HIV-2 antibody positive with target S/CO approximately (b) (4)
- PC HIV5 B, HIV-1 GrpO antibody positive with target S/CO approximately (b) (4)

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys HIV Duo assay. Results were reported as Elecsys HIV Duo (Main Results), the HIVAGB module (HIV-p24 Antigen) and the AHIVB (HIV antibody) separately. The results of the reproducibility panel and control testing demonstrated that the Elecsys HIV Duo assay was reproducible across three sites and three lots of reagents across a range of reactivity (Tables 6 - 8).

Summary Basis for Regulatory Action

Table 6: Overall Repeatability and Reproducibility for Elecsys HIV Duo (Main Result)

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Within-Lab Within-Lot		Between-Lab		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	2.71	270	0.036	1.32	0.017	0.630	0.041	1.53	0.057	2.12	0.000	0.000	0.055	2.03	0.080	2.94
HSP 02	22.3	270	0.313	1.41	0.185	0.832	0.286	1.29	0.463	2.08	0.168	0.753	0.747	3.36	0.895	4.02
HSP 03	2.61	270	0.035	1.34	0.027	1.02	0.036	1.39	0.057	2.19	0.006	0.244	0.187	7.18	0.196	7.51
HSP 04	22.4	270	0.269	1.20	0.176	0.784	0.441	1.97	0.546	2.44	0.000	0.000	0.368	1.64	0.658	2.94
HSP 05	2.63	270	0.041	1.56	0.022	0.819	0.046	1.75	0.065	2.48	0.000	0.000	0.052	1.97	0.083	3.17
HSP 06	3.09	270	0.048	1.54	0.022	0.704	0.039	1.27	0.066	2.12	0.041	1.34	0.103	3.33	0.129	4.17
HSP 07	26.4	270	0.353	1.34	0.191	0.725	0.402	1.52	0.568	2.15	0.260	0.986	0.802	3.04	1.02	3.86
PC HIV1 B G2	0.185	270	0.021	11.6	0.002	0.849	0.008	4.20	0.023	12.3	0.004	2.35	0.017	8.97	0.028	15.4
PC HIV2 B G2	3.62	270	0.058	1.60	0.047	1.31	0.047	1.30	0.088	2.44	0.000	0.000	0.099	2.74	0.133	3.67
PC HIV3 B G2	9.00	270	0.103	1.14	0.118	1.31	0.120	1.33	0.197	2.19	0.062	0.688	0.246	2.73	0.321	3.56
PC HIV4 B G2	4.12	270	0.071	1.74	0.046	1.12	0.064	1.56	0.107	2.59	0.002	0.037	0.217	5.28	0.242	5.88
PC HIV5 B G2	5.96	270	0.114	1.92	0.084	1.40	0.062	1.05	0.155	2.60	0.078	1.30	0.129	2.16	0.216	3.62

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

Table 7: Overall Repeatability and Reproducibility for Elecsys HIV Duo – HIVAGB (Antigen module)

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Within-Lab Within-Lot		Between-Lab		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	0.160	270	0.010	6.10	0.001	0.400	0.006	3.55	0.011	7.07	0.004	2.65	0.014	8.48	0.018	11.4
HSP 02	0.160	270	0.008	5.25	0.003	2.06	0.007	4.66	0.012	7.32	0.006	4.03	0.014	8.84	0.019	12.2
HSP 03	0.158	270	0.009	5.85	0.002	1.20	0.007	4.52	0.012	7.49	0.005	3.40	0.013	8.37	0.019	11.7
HSP 04	0.160	270	0.009	5.49	0.001	0.871	0.007	4.54	0.011	7.18	0.005	3.14	0.014	8.81	0.019	11.8
HSP 05	0.160	270	0.009	5.53	0.003	1.88	0.007	4.31	0.012	7.26	0.004	2.70	0.014	8.89	0.019	11.8
HSP 06	3.09	270	0.047	1.53	0.023	0.733	0.040	1.28	0.066	2.13	0.041	1.34	0.103	3.33	0.129	4.17
HSP 07	26.4	270	0.353	1.34	0.191	0.725	0.402	1.52	0.568	2.15	0.260	0.986	0.802	3.04	1.02	3.86
PC HIV1 B G2	0.169	270	0.010	6.06	0.000	0.000	0.007	4.40	0.013	7.49	0.007	4.10	0.016	9.66	0.022	12.9
PC HIV2 B G2	0.165	270	0.011	6.62	0.000	0.000	0.006	3.92	0.013	7.69	0.005	3.18	0.017	10.5	0.022	13.4
PC HIV3 B G2	9.00	270	0.103	1.14	0.118	1.31	0.120	1.33	0.197	2.19	0.062	0.688	0.246	2.73	0.321	3.56
PC HIV4 B G2	0.165	270	0.010	5.78	0.000	0.000	0.006	3.88	0.011	6.96	0.007	4.02	0.017	10.3	0.022	13.1
PC HIV5 B G2	0.167	270	0.009	5.59	0.002	1.50	0.007	4.10	0.012	7.09	0.005	2.74	0.018	10.5	0.022	13.0

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

Table 8: Overall Repeatability and Reproducibility for Elecsys HIV Duo – AHIVB (Antibody module)

Sample	Mean	N	Repeatability		Between-Ru		Between-Day		Within-Lab Within-Lot		Between-Lab		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	2.70	270	0.036	1.33	0.017	0.616	0.041	1.53	0.057	2.11	0.000	0.000	0.056	2.07	0.080	2.96
HSP 02	22.3	270	0.314	1.41	0.184	0.829	0.287	1.29	0.464	2.08	0.167	0.752	0.748	3.36	0.896	4.03
HSP 03	2.60	270	0.035	1.34	0.026	1.02	0.036	1.39	0.057	2.18	0.007	0.267	0.189	7.25	0.197	7.57
HSP 04	22.4	270	0.270	1.21	0.175	0.782	0.442	1.97	0.547	2.44	0.000	0.000	0.369	1.65	0.659	2.95
HSP 05	2.62	270	0.041	1.58	0.021	0.787	0.046	1.76	0.065	2.49	0.000	0.000	0.053	2.01	0.084	3.20
HSP 06	0.073	270	0.004	5.01	0.000	0.541	0.002	2.45	0.004	5.60	0.002	2.98	0.010	13.5	0.011	14.9
HSP 07	0.079	270	0.004	4.87	0.002	2.06	0.002	2.68	0.005	5.93	0.004	4.61	0.010	12.9	0.012	14.9
PC HIV1 B G2	0.072	270	0.024	33.9	0.002	3.28	0.000	0.000	0.025	34.0	0.002	2.54	0.005	7.36	0.025	34.9
PC HIV2 B G2	3.61	270	0.059	1.62	0.047	1.29	0.047	1.31	0.089	2.45	0.000	0.000	0.099	2.75	0.133	3.69
PC HIV3 B G2	0.069	270	0.003	4.88	0.001	1.71	0.001	2.05	0.004	5.56	0.003	3.84	0.009	12.6	0.010	14.3
PC HIV4 B G2	4.11	270	0.071	1.73	0.047	1.14	0.064	1.56	0.107	2.59	0.000	0.000	0.218	5.30	0.243	5.90
PC HIV5 B G2	5.96	270	0.114	1.92	0.084	1.41	0.063	1.05	0.155	2.61	0.078	1.31	0.129	2.17	0.216	3.63

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

d) 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.

e) Pediatrics

N/A

f) Other Special Populations

N/A

7. Advisory Committee Meeting

N/A

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 March 13, 2023, 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 HIV Duo assay.

b) Risk/Benefit Assessment

The risk/benefit analysis demonstrates that the benefit of the Elecsys HIV Duo 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 99.81% – 100.00%), indicating a low probability of a false negative result. Among 17,168 blood and plasmapheresis donors tested with the Elecsys HIV Duo assay, the assay specificity of 99.92% (95% CI of 99.86 – 99.95%) in clinical trials suggests a low probability of a false positive result. When licensed, this will be the first FDA approved antigen-antibody combo donor screening assay that detects and differentiates reactivity to p24 antigen and antibodies to HIV (HIV-1 groups M and O, and HIV-2).

c) Recommendation for Postmarketing Activities

No postmarketing activities have been proposed for this application.