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 Template

Date: February 21, 2024

From: Krishna Mohan V. Ketha, Ph.D.,
Chair of the Review Committee

BLA/ STN#: 125802/0

Applicant Name: Roche Diagnostic Solutions
9115 Hague Road; Indianapolis, IN 46256

Date of Submission: April 24, 2023

MDUFA Goal Date: February 22, 2024

Proprietary Name: Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm

Intended Use for Elecsys HBsAg II:
Elecsys HBsAg II is an in vitro immunoassay for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum and plasma. Elecsys HBsAg II 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 **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.

Intended Use for Elecsys HBsAg II Auto Confirm:
Elecsys HBsAg II Auto Confirm is an in vitro immunoassay for the qualitative confirmation of the presence of hepatitis B surface antigen (HBsAg) in human serum and plasma samples repeatedly reactive when tested with the Elecsys HBsAg II assay. Elecsys HBsAg II Auto Confirm is intended to confirm HBsAg presence in individual human donors, including volunteer donors of whole blood, blood components and source plasma.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "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, M.D., Director, Office of Blood Research and Review

X 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.

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*	 Krishna Mohan V. Ketha Ragupathy Viswanathan David McGivern Nitin Verma Xue Wang	 February 9, 2024 December 13, 2023 December 20, 2023 January 3, 2024 June 15, 2023
Living Organ Donor, and Cadaveric Donor Claim *(OTP/DHT)*	Hahn Khuu	January 10, 2024
Statistical Review • *Clinical and Non-Clinical (OBPV/DB/DNCE)*	Paul Hshieh	September 21, 2023
CMC Review • *CMC (OBRR/DETTD)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DMPQ)*	 Mohan Haleyurgirisetty Kavita Singh Prajakta Varadkar Hyesuk Kong	 January 2, 2024 January 19, 2024 January 18, 2023 November 24, 2023
Labeling Review(s) • *APLB (OCBQ/APLB)* • *Product Office (OBRR/DETTD)*	 Sadhna Khatri Krishna Mohan V. Ketha	 December 11, 2023 February 9, 2024
Lot Release Protocols/Testing Plans (*OCBQ/DBSQC*)	Selwyn Wilson-David	February 20, 2024
Bioresearch Monitoring Review (*OCBQ/BIMO*)	Kanaeko Ravenell	January 12, 2024
Software and Instrumentation *(OBRR/DETTD)*	Hongqiang Hu	December 28, 2023

1. Introduction

The Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4), Germany. This biologics license application (BLA) for Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay from Roche Diagnostics Solutions, 9115 Hague Road Indianapolis, IN 46250, USA was received on April 24, 2023.

The application was assigned the number STN 125802/0 and granted a standard 10-month review status with a goal date of February 22, 2024. The application was filed May 25, 2023, and the mid-cycle meeting took place on September 19, 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
April 24, 2023	Original BLA received	BL125802/0
May 9, 2023	Software Update Version 1.0.3 to Version 1.1	BL125802/0/1
May 18, 2023	Correct Facility FEI/DUNS number	BL125802/0/2
June 5, 2023	Information Request (IR) for data location	BL125802/0/3
June 20, 2023	IR – Lot Release Protocol template	BL125802/0/4
June 22, 2023	Revised Label sets submitted by RD	BL125802/0/5
August 09, 2023	IR – AET and Bioburden study	
August 23, 2023	Response to IR of 08/09/23	BL125802/0/7
September 18, 2023	IR – CMC clarification for documentation	
September 22, 2023	Response to IR of 09/18/23	BL125802/0/8
September 27, 2023	Address for Blinded Panels	BL125802/0/9
September 29, 2023	Lot Release Templates	BL125802/0/10
October 25, 2023	Bioburden results	BL125802/0/11
November 27, 2023	IR – Analytical studies clarification	
November 30, 2023	Response to IR of 11/27/23	BL125802/0/12
January 6, 2024	IR – Environmental impact clarification	
January 6, 2024	Response to IR of 01/06/24	BL125802/0/13
February 7, 2024	IR – Updating Package Inserts/Labels	
February 8, 2024	IR – consistent units for LoB/LoD study	
February 9, 2024	Response to IR of 02/08/24	BL125802/0/14
February 9, 2024	Blinded Panel Results	BL125802/0/15
February 16, 2024	Updates to Package Inserts/Labels	BL125802/0/16

2. Background

The Elecsys HBsAg II assay is a qualitative, serological, sandwich immunoassay for the detection of hepatitis B surface antigen in human serum and plasma. The Elecsys

HBsAg II Auto Confirm assay is a qualitative, serological, sandwich immunoassay for the confirmation of HBsAg presence in human serum and plasma samples repeatedly reactive when tested with the Elecsys HBsAg II assay. HBsAg is detected using a mixture of monoclonal and polyclonal anti-HBsAg antibodies 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 HBSAG2B 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 <0.90 are considered non-reactive for HBsAg and do not need further testing. Samples with a COI ≥0.90 are considered initially reactive on the Elecsys HBsAg II. All serum and plasma samples that are initially reactive are automatically retested in duplicate using the Elecsys HBsAg II assay. All HBsAg repeat reactive samples are tested by HBsAg II Auto Confirm. 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 manufacturing of the Elecsys HBsAg II assay and Elecsys HBsAg II Auto Confirm assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay is manufactured at the Roche Diagnostics GmbH facilities in Germany located at (b) (4) Sandhofer Strasse 116, Mannheim, 68305, Germany. The third manufacturing site is located at Roche Diagnostics Operations (b) (4) .

The Elecsys HBsAg II test kit (List Number 08814848162) consists of 20 reagent cassettes (**cobas e** pack), each containing components M, R1, and R2, and two

identical calibrator packs, each containing the components HBSAG2B Cal1 and HBSAG2B 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-) Anti-HBsAg antibodies
- HBSAG2B Cal1: Non-reactive calibrator 1, human serum non-reactive for HBsAg
- HBSAG2B Cal2: Reactive calibrator 2, human serum reactive for HBsAg

The Elecsys HBsAg II Auto Confirm test kit (List Number 08741034162) consists of two **cobas e** packs (labeled as HBSAGACB) containing components M, R1, and R2 (same reagents as Elecsys HBsAg II), pretreatment **cobas e** pack containing PT1 (confirmatory pretreatment) and PT2 (control pretreatment), and four calibrator bottles ((2) HBSAGACB Cal1 and (2) HBSAGACB Cal2), which are identical to calibrators of Elecsys HBsAg II.

PreciControl HBsAg II (List Number 04687876162), supplied separately, is used for quality control of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm. The control kit consists of the following components:

- PC HBSAG1B: Negative Control, human serum non-reactive to HBsAg
- PC HBSAG2B: Positive Control, human serum reactive to HBsAg

PreciControl HBsAg Auto Confirm (List Number 08741107162) is used as quality control for the pretreatment function of Elecsys HBsAg II Auto Confirm. The kit consists of one component (PC HBSAGCB), which is identical to PC HBSAG2B and is supplied separately.

PreciControl Release HBsAg II (List Number 09366717190), is identical to PC HBSAG2B, supplied separately, is used as a Release Control and consists of one component (PC HBSAGR), which contains human serum reactive for HBsAg.

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 validation and/or qualifications reviewed for the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay components 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 performed and inspectional history for the facility involved in the manufacturing of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm are summarized in the table below and are further described in the paragraphs that follow.

Table 3: Manufacturing facility details for Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm

Manufacturing/ Testing Activities	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)	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) (3) ; VAI ORA For-Cause Inspection August 2019; VAI ORA Post-Market Approval Inspection April 2018; NAI

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

Office of Regulatory Affairs (ORA) performed a post-market approval inspection at Roche Diagnostics GmbH, Mannheim, Germany in April 2018. The inspection covered Elecsys assay kits. No FDA Form-483 was issued, and the inspection was classified as No Action Indicated (NAI).

Roche Diagnostics GmbH, Mannheim, Germany
The ORA/Office of Pharmaceutical Quality Operations performed a MRA review of a foreign surveillance inspection in (b) (3) at Roche Diagnostics GmbH, Mannheim, Germany. 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 August 2019. 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 April 2018. The inspection covered Elecsys assay kits. No FDA Form-483 was issued and the inspection was classified as NAI.

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 System

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 publication 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 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 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 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 HBsAg II and Elecsys HBsAg II Auto Confirm 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 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 HBsAg II and Elecsys HBsAg II Auto Confirm 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.

Review Note: As agreed in BQ170139/1, 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 HBsAg II and Elecsys HBsAg II Auto Confirm BLA are not impacted by this update.

5. Analytical Studies

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

a) Precision

This study was conducted to evaluate repeatability (within run precision) and intermediate precision (within laboratory precision) according to CLSI EP05-A3.

<u>Elecsys HBsAg II</u>

Precision of the Elecsys HBsAg II assay was evaluated using one lot of the Elecsys HBsAg II and one lot of PreciControl HBsAg. Testing was performed over 21 days, with one run per day, using two replicates, for a total of 84 measurements per sample. The panel members included:

- One HBsAg non-reactive sample, (b) (4) S/CO
- One HBsAg non-reactive sample, (b) (4) S/CO

- Three HBsAg reactive samples, (b) (4) S/CO
- One HBsAg high-reactive sample, (b) (4) S/CO
- PreciControl HBSAG1B at target level (b) (4) S/CO
- PreciControl HBSAG2B at target level (b) (4) S/CO

Table 4: Intermediate (Within-Laboratory) Precision of Elecsys HBsAg II

Sample	Mean COI	N	Repeatability		Within-Laboratory Precision	
			SD	CV (%)	SD	CV (%)
HSP1	0.254	84	0.018	7.1	0.030	11.7
HSP2	0.784	84	0.030	3.8	0.038	4.80
HSP3	0.962	84	0.038	4.0	0.045	4.70
HSP4	1.12	84	0.036	3.3	0.043	3.90
HSP5	1.22	84	0.036	2.9	0.046	3.80
HSP6	10.8	84	0.295	2.7	0.365	3.40
PC HBsAg 1	0.363	84	0.036	9.9	0.040	11.0
PC HBsAg 2	4.17	84	0.091	2.2	0.125	3.00

HSP=Human Specimens; PC= PreciControls; N = number of replicates; CV = coefficient of variation expressed as a percentage; SD = standard deviation

Elecsys HBsAg II Auto Confirm

Precision of the Elecsys HBsAg II Auto Confirm assay was evaluated using one lot of the Elecsys HBsAg II Auto Confirm and one lot of PreciControl HBsAg. Testing was performed over 21 days, with one run per day, using two replicates, for a total of 84 measurements per sample. The panel members included:

- One low HBsAg reactive sample (b) (4) S/CO in Elecsys HBsAg II
- Three moderate HBsAg reactive (b) (4) S/CO in Elecsys HBsAg II
- One high HBsAg reactive (b) (4) S/CO in Elecsys HBsAg II
- One reactive PreciControl HBsAg Auto Confirm, approximately (b) (4) S/CO

Table 5: Intermediate (Within-Laboratory) Precision of Elecsys HBsAg II Auto Confirm

Sample	Mean COI	N	Repeatability		Within-Laboratory Precision	
			SD	CV (%)	SD	CV (%)
HSP1	0.443	84	0.038	8.6	0.049	11.1
HSP2	1.06	84	0.104	9.9	0.127	12.0
HSP3	16.8	84	0.963	5.7	1.06	6.3
HSP4	0.071	84	0.005	6.4	0.005	7.0
HSP5	33.0	84	3.24	9.8	4.48	13.6
PC HBsAg 2	8.97	84	0.748	8.3	0.780	8.7

b) Limit of Detection

(b) (4)

(b) (4)

c) Analytical Sensitivity

Elecsys HBsAg II

For determination of the cut-off sensitivity, a dilution series of two HBsAg reference standards (WHO standard 00/588, 2nd International Standard for HBsAg. Subtype adw2. Genotype A, and WHO standard 12/226, 3rd International Standard for HBsAg, HBV genotype B4, HBsAg subtype ayw1/adw2) were prepared. The measurements were performed in duplicate with three reagent lots (lots (b) (4)), on one **cobas e** 801 analyzer, at one site. The data demonstrate acceptable performance of the assay; the results from three kit lots at the S/CO of 0.90 were 0.023, 0.027, and 0.028 IU/mL (average 0.026 IU/mL) for NIBSC code 00/588 and 0.025, 0.026, and 0.028 IU/mL (average 0.026 IU/mL) for NIBSC code 12/226.

Elecsys HBsAg II Auto Confirm

This study was conducted to confirm the cut-off sensitivity of Elecsys HBsAg II Auto Confirm assay. For the study, (b) (4) dilution steps of the Second International Standard (WHO standard 00/588) were determined in (b) (4) , while (b) (4) dilution steps of the Third International Standard (WHO standard 12/226) were determined in (b) (4) with the control and the confirmatory reaction. The measurements were performed using (b) (4) Elecsys HBsAg Auto Confirm reagent lots (lots (b) (4)), on (b) (4) , at (b) (4) . The data demonstrate acceptable performance of the assay; the results from (b) (4) kit lots with the Elecsys HBsAg II mean S/CO of (b) (4) was 0.0390 IU/mL for NIBSC code 00/588 and 0.0370 IU/mL for NIBSC code 12/226.

d) Seroconversion Sensitivity

The seroconversion sensitivity of Elecsys HBsAg II assay and Elecsys HBsAg II Auto Confirm was compared to the sensitivity of an FDA-licensed assay. (b) (4) each of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm was used on (b) (4) **cobas e** 801 analytical units to test a total of 20 seroconversion panels. For 19 of the 20 panels, the first reactive time point for the Elecsys HBsAg II assay occurred at the same time as the first reactive time point for the comparator assay. One panel demonstrated earlier detection by one bleed compared to the comparator

assay. Among the 19 concordant panels there was one panel (Panel 10) that had reactivity in the day 0 bleed by the comparator assay and was non-reactive by the Elecsys HBsAg II. This sample was non-reactive on the Elecsys HBsAg II Auto Confirm assay (Table 6). Later samples in this panel were concordant. The summary of the results across the 20 seroconversion panels is presented below.

Table 6: Seroconversion sensitivity of Elecsys HBsAg II and Elecsys HBsAg Auto Confirm

S. No.	Panel ID	Difference in number of bleeds (+/-)	Elecsys HBsAg II first reactive result (bleed number)	Reference method first reactive result (bleed number)	Reactivity status by Elecsys HBsAg II AC
1	HBV6271	0	3	3	Reactive
2	HBV6272	0	20	20	Reactive
3	HBV6274	0	1	1	Reactive
4	HBV6276	0	7	7	Reactive
5	HBV6277	0	6	6	Reactive
6	HBV6279	0	6	6	Reactive
7	HBV6286	0	5	5	Reactive
8	HBV6292	0	7	7	Reactive
9	HBV9072	0	12	12	Reactive
10	HBV9073	0	N/A	1*	Non-reactive
	HBV9073	0	14	14	Reactive
11	HBV9074	0	17	17	Reactive
12	HBV11002	0	3	3	Reactive
13	HBV11011	0	9	9	Reactive
14	HBV11012	0	4	4	Reactive
15	HBV11016	0	6	6	Reactive
16	HBV11024	0	11	11	Reactive
17	HBV11029	0	9	9	Reactive
18	HBV11058	0	5	5	Reactive
19	HBV11059	-1	5	6	Reactive
20	HBV11069	0	9	9	Reactive

*The HBsAg reactive result by the reference method was found to be HBsAg non-reactive by the Elecsys HBsAg II AC and determined to be discrepant.

e) Mutant Recognition Study

This study was performed to demonstrate the ability of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assays to detect recombinant mutants and native samples containing HBsAg mutants. Samples for the study included 20 recombinant HBsAg proteins with mutations and (b) (4) native samples with HBsAg mutations and testing was performed using (b) (4) of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm, and samples were measured in (b) (4) determinations. All (b) (4) native samples with HBsAg mutations (Table 7) and all 20 recombinant mutant samples (Table 8) were detected by the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay.

Table 7: Native HBsAg mutant recognition by Elecsys HBsAg II and Elecsys HBsAg Auto Confirm

(b) (4)

Table 8: Recombinant HBsAg mutant recognition by Elecsys HBsAg II and Elecsys HBsAg Auto Confirm

Sample	Mutation	Elecsys HBsAg II reactivity	Elecsys HBsAg II AC reactivity
Mutant 1	F8L, R24K, N40S, G43R, L94S, M103I, 113A114, M133T, P142L, D144G	+	+
Mutant 2	T/A45S, C107R, M195I	+	+
Mutant 3	S132Y, P142S, G145R	+	+
Mutant 4	T123N	+	+
Mutant 5	G145K	+	+
Mutant 6	D144G	+	+
Mutant 7	D144A	+	+
Mutant 8	G145R	+	+
Mutant 9	122RA123	+	+
Mutant 10	Q129P, F134R, P142L, D144E, G145K, S171F, L175S	+	+
Mutant 11	R122I	+	+
Mutant 12	M125T, T127P, P142A, G145R	+	+
Mutant 13	T131I	+	+
Mutant 14	C147S	+	+
Mutant 15	K141E	+	+
Mutant 16	S143L	+	+
Mutant 17	P142L	+	+
Mutant 18	Y134S	+	+
Mutant 19	E164D	+	+
Mutant 20	I126S	+	+

f) Endogenous Interferences (Spiked)

Assay performance of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm was evaluated in samples with high levels of spiked interferants (hemoglobin, lipemia, bilirubin, and human serum albumin for total protein) using (b) (4) The data demonstrate acceptable performance of the assay for both nonreactive and reactive samples, supporting the use Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assays with donor specimens containing up to 500 mg/dL of hemoglobin, 2000 mg/dL lipid, 44 mg/dL bilirubin, and 7 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 1,200 ng/mL of biotin using the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assays.

g) Endogenous Interferences (Native)

Assay performance of Elecsys HBsAg II 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 demonstrate acceptable performance of the assay supporting the use of specimens that contain up to (b) (4) of hemoglobin (range tested (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)).

h) Human Anti-Sheep (HASA) Effect

This study evaluated the potential HASA interference with Elecsys HBsAg II Auto Confirm. (b) (4)

i) Drug Interference

Potential interference with the Elecsys HBsAg II assay and Elecsys HBsAg II Auto Confirm assays from common therapeutic drugs was tested using HBsAg negative and positive samples spiked individually with the following drugs: (b) (4)

(b) (4). No interference with Elecsys HBsAg II and Elecsys HBsAg II Auto Conform assay was detected from the drugs tested at concentrations of at least (b) (4) times the highest blood concentration observed under therapeutic treatment ((b) (4)).

j) Cross Reactivity/Analytical Specificity

The performance of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assays when used to test specimens containing potential cross reactants (medical condition/ pathogen not related to HBV infection) or from risk groups causing interferences to infectious disease assays was evaluated. A total of 311 samples were tested with at least (b) (4) samples from each group. The effect of potentially interfering factors was tested with specimens containing:

- Containing antibodies against acute HAV (anti-HAV (b) (4)), anti-HAV (b) (4), HSV (b) (4), EBV ((b) (4)), EBV ((b) (4)), anti-HEV, anti-*Escherichia coli*, anti-Candida positive, anti-Chlamydia positive, HAMA (heterophilic), (b) (4)
- From pregnant individuals with both single and multiparous pregnancy
- Containing Anti-Nuclear Antibodies (ANA)
- Containing autoimmune antibodies: Morbus Crohn, and Colitis Ulcerosa
- After vaccination against Hepatitis A, (b) (4) and influenza
- From patients with HIV, HCV, HTLV- I/II, HDV, VZV, *Parvovirus B19*, Rubella, *Toxoplasma gondii*, *Treponema pallidum* (Syphilis) infection
- From patients with alcohol-induced hepatitis/ cirrhosis
- From patients with systemic lupus erythematosus (SLE)

The data demonstrate acceptable performance of the assay as the presence of potentially interfering substances or medical conditions had no effect on the detection of HBsAg. There was no significant effect on background signals in negative specimens (neat specimens).

k) Prozone (Hook Effect)

Elecsys HBsAg II

The effect of high dose or concentration of HBsAg on the performance of the Elecsys HBsAg II assay was evaluated. (b) (4) Study was conducted using (b) (4) of Elecsys HBsAg II, on (b) (4), at (b) (4), using (b) (4) measurements. The data provided demonstrate acceptable performance of the assay as all high titer specimens tested reactive. No false non-reactive results, due to hook effect, were observed for samples up to HBsAg concentration of 1.5 x 10^6 IU/mL.

Elecsys HBsAg II Auto Confirm

(b) (4)

l) Serum and Plasma Comparison

The impact of anticoagulants on the performance of the Elecsys HBsAg II and Elecsys HBsAg II Autoconfirm assays was evaluated using (b) (4) matched serum and plasma specimens collected from individual donors. Reactive samples and near cut-off non-reactive samples were contrived by (b) (4) . (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 (K_2-EDTA), tri-potassium EDTA (K_3-EDTA) and citrate phosphate dextrose (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-, K_2-EDTA- and lithium heparin separation tubes. The data provided and reviewed demonstrate acceptable performance of the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay with specimens collected in the anticoagulants and tube types listed above supporting the use of specimens collected in these anticoagulants and tube types.

m) Specimen Storage

Performance of the Elecsys HBsAg II assay with serum and plasma specimens collected in K_2-EDTA, sodium citrate, lithium heparin and CPD stored at various temperatures for different periods of time was evaluated. The target analyte concentrations ranged from (b) (4) to (b) (4) COI for negative and (b) (4) to (b) (4) COI for HBsAg positive samples.

The data demonstrate acceptable performance of the Elecsys HBsAg II assay supporting the use of serum and plasma samples that were stored at 15 to 25°C for up to 7 days, 2 to 8°C for up to 14 days, -20°C for up to 1 month, and up to 4 freeze/thaw cycles. These data support the storage claims in the package insert.

n) Specimen Processing

Assay performance of Elecsys HBsAg II with centrifuged non-frozen and previously frozen specimens was evaluated using (b) (4) serum specimens – HBsAg negative (n=(b) (4)) or spiked with HBsAg (n=(b) (4)) low positive, and with HBsAg (n=(b) (4))

high positive – compared to the uncentrifuged, homogenized reference. The target concentrations ranged from (b) (4) to (b) (4) S/CO. The data demonstrate acceptable performance of the Elecsys HBsAg II 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).

o) On-clot Sample Stability

Assay performance of Elecsys HBsAg II with serum and plasma (K_2-EDTA, sodium citrate and lithium heparin) specimens after storage on-clot was evaluated using (b) (4) non-reactive and (b) (4) HBsAg reactive specimens and compared to specimens stored at unstressed conditions. The target concentrations ranged from (b) (4) to (b) (4) S/CO. The data demonstrate acceptable performance of the Elecsys HBsAg II assay supporting the use with samples stored on-clot for up to 7 days at 15 to 30°C and up to 14 days at 2 to 8°C.

p) Kit Lot Calibration and On-Board Calibration Stability

Calibration must be performed once per reagent lot using HBSAGB Cal1 and HBSAGB Cal2 for the Elecsys HBsAg II assay and HBSAGACB Cal1 and HBSAGACB Cal2 for the Elecsys HBsAg II Auto Confirm assay. Lot calibration stability was validated using (b) (4) each of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm kits stored at 2 to 8°C up to (b) (4) weeks using the initial calibration. A total of (b) serum specimens – HBsAg negative (n=(b) (4)) and HBsAg low and high positive (n=(b) (4)) at analyte level ranging from (b) (4) COI to (b) (4) COI 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 demonstrate acceptable performance of the assay supporting a Lot Calibration stability of up to 12 weeks. In addition, the same panel was utilized to test stability of the Elecsys HBsAg II kit and Elecsys HBsAg II Auto Confirm 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.

q) Reagent Stability Studies

Elecsys HBsAg II

Reagent real time stability was validated using (b) (4) Elecsys HBsAg II kit lots stored at 2 to 8°C up to (b) (4) months compared to t = 0 months. A total of (b) (4) specimens – HBsAg non-reactive (n=(b) (4)), close to cutoff (n=(b)), low and high reactive (n=(b) (4)) at the reactivity range from (b) (4) S/CO to (b) (4) S/CO along with (b) (4) PreciControls - were tested in (b) (4) and compared to unstressed reagents. The data demonstrate acceptable performance of the assay supporting a reagent stability claim of up to 24 months at 2 to 8°C. In addition, the same panel was utilized to evaluate on-board stability of the Elecsys HBsAg II components when stored at 2 to (b) (4) °C for (b) (4) weeks. Transport stability was evaluated at (b) (4) for (b) (4) and 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 2 to (b) (4) °C and a transportation claim of up to (b) (4) (b) (4) at (b) (4).

Elecsys HBsAg II Auto Confirm

Reagent real time stability was validated using (b) (4) Elecsys HBsAg II Auto Confirm kit lots stored at 2 to 8°C up to (b) (4) months compared to t = 0 months. A total of (b) (4) reactive specimens – HBsAg low reactive (b) (4) COI, (b) (4) reactive (b) (4) COI and high reactive (b) (4) COI on Elecsys HBsAg II and (b) (4) PreciControl HBsAg Auto Confirm - were tested in (b) (4) and compared to unstressed reagents. The data demonstrate acceptable performance of the assay supporting a reagent stability claim of up to 24 months at 2 to 8°C. In addition, the same panel was utilized to evaluate on-board stability of the Elecsys HBsAg II Auto Confirm components when stored at 2 to 8°C for (b) (4) weeks and at (b) (4) for (b) 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) at (b) (4).

r) Calibrator Stability

Calibrators are supplied ready-for-use in vials compatible with the system. The composition and packaging of the calibrators are the same for the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay. Stability of calibrators was evaluated by measuring them in duplicate after storage under various conditions. The data demonstrate acceptable performance of calibrators supporting stability claims of storage for up to 5 hours at 20 to 25°C, and up to 16 weeks at 2 to 8°C.

s) PreciControl Stability

Elecsys HBsAg II

The PreciControl HBsAg II is supplied as ready-for-use in vials used for monitoring the accuracy of the Elecsys HBsAg II assay. Stability of PreciControl (PC) HBSAG1B and PC HBSAG2 B was evaluated after storage under various conditions compared to t = 0 by (b) (4) measurements. The data demonstrate acceptable performance of calibrators supporting stability claims of storage at 20 to 25°C for up to 5 hours, at 2 to 8°C for up to 7 days after opening, and a shelf-life of 19 months at 2 to 8°C. Multiple-use stability data were acceptable for up to (b) (4) quality control procedures when stored at 20 to 25°C.

Elecsys HBsAg II Auto Confirm

The PreciControl HBsAg II Auto Confirm is supplied as ready-for-use in vials used for monitoring the accuracy of the Elecsys HBsAg II Auto Confirm assay. Stability of PreciControl (PC) HBSAGCB was evaluated after storage under various conditions compared to t = 0 by (b) (4) measurements. The data demonstrate acceptable performance of calibrator supporting stability claims of storage at 20 to 25°C for up to 5 hours, at 2 to 8°C for up to 7 days after opening,

transport stability for (b) (4) at (b) (4), and a shelf-life of 18 months at 2 to 8°C. Multiple-use stability data were acceptable for up to (b) (4) quality control procedures when stored at 20 to 25°C.

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

Performance of the Elecsys HBsAg II assay when used to test specimens, calibrators, and controls directly after storage at 2 to 8°C was evaluated using (b) (4) negative serum samples and (b) (4) serum samples spiked with reactive source material were measured in (b) (4), compared to samples that were equilibrated at (b) (4). The data demonstrate acceptable performance of the Elecsys HBsAg II assay supporting the use of specimens and kit components without first equilibrating for (b) (4).

u) Within-Assay Carryover

Sample to sample carryover was evaluated with the HBsAg II assay using a panel of (b) (4) high HBsAg positive and (b) (4) HBsAg negative samples run (b) (4) times on (b) (4) **cobas e** 801 analyzers. Every negative sample was exposed to potential carryover (b) (4) times. After sample processing, all negative samples were retested and yielded concentrations below the HBsAg II assay LoD of (b) (4). No sample-to-sample carryover was detected.

v) Cadaveric Studies

No cadaveric claims were sought by the Sponsor in this BLA.

w) Microbial Challenge

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

6. Clinical Studies

Elecsys HBsAg II

A prospective multisite study was performed to evaluate assay specificity, sensitivity, and reproducibility to demonstrate performance of the Elecsys HBsAg II Assay in the intended use population. Testing was performed at four blood donor testing laboratories using specimens collected from four whole blood collection sites, six commercial specimen vendors, four internal specimen inventories, and one plasmapheresis collection site. Four lots of the Elecsys HBsAg Reagent Kit, two lots each of the PreciControl HBsAg II and the PreciControl HBsAg II Release Kit, and four lots of the Elecsys HBsAg II Auto Confirm Reagent Kit were used for the studies at testing sites. Two FDA-licensed confirmatory assays were used as the comparator tests.

Test results from Elecsys HBsAg II on the cobas pro serology solution were either compared directly against the comparator assay (sensitivity cohorts) or against the final HBsAg specimen status (specificity donor population and the increased risk / HBV

recovered cohorts). Specimen status was established by confirmatory/supplemental testing according to a predefined testing algorithm. For the testing algorithm two nucleic acid testing methods were used due to the availability of these assays at the testing centers.

Elecsys HBsAg II Auto Confirm

The Elecsys HBsAg II Auto Confirm is used primarily for confirming HBsAg reactivity status of all HBsAg repeat reactive samples determined by Elecsys HBsAg II assay. Therefore, the performance of this assay was demonstrated by evaluating Elecsys HBsAg repeat reactive specimens obtained from the specificity cohorts (donor population, increased risk, and HBV recovered patients) and the sensitivity cohorts (known HBsAg positives from various disease categories).

a) Clinical Specificity of the HBsAg II assay

Clinical specificity of the Elecsys HBsAg II assay on the **cobas e** 801 analyzer was evaluated by using an FDA-licensed comparator assay and testing a total of 14,284 specimens in a prospective multisite study. All repeatedly reactive (RR) specimens determined by Elecsys HBsAg II were tested using the Elecsys HBsAg II Confirm assay. All donors enrolled were evaluated and no donation was excluded.

A total of 14,284 voluntary blood donor specimens (5,569 serum specimens, 5,713 plasma specimens, and 3,002 plasmapheresis samples) were collected at four blood donation centers and testing was performed at four (b) (4) sites. For Elecsys HBsAg II the initial reactive rate was 0.05% (7/14,284), and the repeat reactive rate was 0.04% (6/14,284). The initial and repeat reactive rate for the comparator was 0.05% (7/14,284). Repeatedly reactive (RR) specimens were tested using the Elecsys HBsAg II Confirm assay.

One specimen that was repeatedly reactive on both Elecsys HBsAg II and the comparator was reactive on the Elecsys HBsAg II Auto Confirm assay (Table 9) and confirmed by an FDA-licensed HBV Qualitative NAT assay. The final status of this specimen was interpreted as HBsAg positive, and this specimen was excluded from the specificity calculations. The 5 repeat reactive (RR) specimens that were not reactive on the Elecsys HBsAg II Auto Confirm assay were nonreactive by an FDA-licensed HBsAg assay. Eleven specimen results were discordant between Elecsys HBsAg II and the comparator – of which five specimens were repeatedly reactive on the Elecsys assay and non-reactive on the comparator, while 6 specimens were nonreactive on the Elecsys HBsAg II assay and repeatedly reactive on the comparator. Supplemental confirmatory testing indicated that there were 5 false reactive results with 14,278 congruent negative specimens for the Elecsys HBsAg II assay and 6 false reactive results with 14,277 congruent negative specimens for the comparator assay.

The overall specificity of the Elecsys HBsAg II in blood and plasmapheresis donors was calculated to be 99.96% (14,278/14,283) with a 95% confidence interval of 99.92% to 99.99% (Table 9).

Table 9: Clinical Specificity of Elecsys HBsAg II in Donors

Specimen Category	Number Tested	Initially Reactive (% of Total)	Repeatedly Reactive (RR) (% of Total)	Reactive by Elecsys HBsAg II Auto Confirm (% of RRs)	Number Confirmed Positive* (% of RR)	% Specificity (95% CI)
Voluntary Blood Donors -Serum	5,569	1 (0.02)	1 (0.02)	0 (0.00)	0 (0.00)	99.98 (5,568/5,569) (99.90 – 100.00)
Voluntary Blood Donors -Plasma	5,713	4 (0.07)	3 (0.05)	1 (33.33)	1 (33.33)	99.96 (5,710/5,712) (99.87 – 99.99)
Total Voluntary Blood Donors	**11,282**	**5** (0.04)	**4** (0.04)	**1** (25.00)	**1** (25.00)	**99.97 (11,278/11,281)** (99.91 – 100.00)
Plasmapheresis Donors	3,002	2 (0.07)	2 (0.07)	0 (0.00)	0 (0.00)	99.93 (3,000/3,002) (99.76 – 99.98)
Total Donors	**14,284**	**7** (0.05)	**6** (0.04)	**1** (16.67)	**1** (16.67)	**99.96 (14,278/14,283)** (99.92 – 99.99)

*Number confirmed positive by supplemental testing; CI = confidence interval

b) Clinical Sensitivity

Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assay sensitivity was established by analyzing test results for 582 specimens that were identified as HBsAg positive. All samples were analyzed on both the Elecsys HBsAg II assay and the comparator assay. Testing was performed at three clinical sites. Elecsys HBsAg II repeatedly reactive specimens were tested with Elecsys HBsAg II Auto Confirm and were confirmed positive by an FDA-licensed assay. All repeat reactive (RR) specimens detected using the Elecsys HBsAg II or the comparator assay were tested with their respective confirmatory assays. Only samples that were repeatedly reactive with the comparator assay were included in the sensitivity analysis. Samples that were nonreactive with the assay were excluded from the study.

The overall sensitivity of Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm was determined to be 100% (582/582) for preselected positives with a 95% confidence interval of 99.34% to 100.00%. All specimens were reactive on the Elecsys HBsAg II Auto Confirm assay (Table 10).

Table 10: Clinical Sensitivity of Elecsys HBsAg II and Elecsys HBsAg II AC

Specimen Category	Number Tested	Repeatedly Reactive (RR) (% of Total)	Reactive by Elecsys HBsAg II AC (% of RRs)	Percent of RR Confirmed Positive* (95% CI)
Acute HBV	80	80 (100)	80 (100)	100 (95.42 – 100.00)
Chronic HBV	186	186 (100)	186 (100)	100 (97.98 – 100.00)
HBsAg (Genotypes A-H)	19	19 (100)	19 (100)	100 (83.18 – 100.00)
HBsAg positive	297	297 (100)	297 (100)	100 (98.72 – 100.00)
Total	582	582 (100)	582 (100)	100 (99.34 – 100.00)

*Number confirmed positive by comparator testing; CI = confidence interval

c) Reactivity in Increased Risk Populations and Endemic Areas

Elecsys HBsAg II performance in an untested increased risk (n=409) and HBV recovered (n=53) population was evaluated using a total of 462 specimens

All repeatedly Elecsys HBsAg II reactive specimens were tested on Elecsys HBsAg II Auto Confirm. Recovered HBV infection specimens were assumed HBsAg negative and were not included in the sensitivity analysis. There were two specimens from individuals at increased risk of HBV infection that were repeatedly reactive with the Elecsys HBsAg II and comparator assay and were confirmed positive by supplemental testing (Table 11).

Table 11. Clinical Sensitivity of Elecsys HBsAg II and Elecsys HBsAg II AC in Increased Risk and Recovered HBV Cohorts

Specimen Category	Number Tested	Repeatedly Reactive (RR) (% of Total)	Reactive by Elecsys HBsAg II AC (% of RRs)	Number Confirmed Positive* (% of RR)[a]
Increased risk for hepatitis infection	409	4 (0.98)	2 (50.0)	2 (50.0)
HBV recovered	53	1 (1.89)	0 (NA)	0 (NA)
Total	462	5 (1.08)	2 (40.0)	2 (40.0)

*Number confirmed positive by supplemental testing; a = the sensitivity and 95% confidence intervals are not estimated due to the small sample size

d) Reproducibility Studies

Elecsys HBsAg II

Reproducibility of the Elecsys HBsAg II assay was evaluated at three sites with (b) (4) per site using three lots each of the Elecsys HBsAg II assay and one lot each of PreciControl HBsAg II 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 HBsAg II kits yielding 270 test results per panel member (2 runs/day x 5 days x 3 replicates/concentration x 3 sites x 3 reagent lots). The member panel included:

- (b) (4) low HBsAg reactive sample at the target S/CO (b) (4)
- (b) (4) high HBsAg reactive sample at target S/CO (b) (4)

Additionally, (b) (4) lots of PreciControls were tested as samples:

- PreciControl HBSAGCB at target level S/CO (b) (4)

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys HBsAg II assay. The results of the reproducibility panel and control testing demonstrate that Elecsys HBsAg II assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 12.

Table 12. Overall repeatability and reproducibility for Elecsys HBsAg II

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Intermediate Precision		Between-Site		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	1.74	270	0.067	3.85[B]	0.009	0.492	0.024	1.38	0.072	4.12[B]	0.030	1.75	0.123	7.07	0.146	8.37[B]
HSP 02	7.04	270	0.182	2.59[B]	0.092	1.31	0.145	2.06	0.250	3.56[B]	0.149	2.12	0.601	8.54	0.668	9.49[B]
PreciControl HBSAG1B	0.411	270	0.030[A]	7.28[B]	0.000	0.000	0.014	3.45	0.033[A]	8.06[B]	0.012	2.89	0.018	4.46	0.040[A]	9.65[B]
PreciControl HBSAG2B	3.81	270	0.098	2.56[B]	0.025	0.642	0.059	1.56	0.117	3.07[B]	0.067	1.76	0.382	10.0	0.405	10.6[B]

[A.] Precision result used in comparison to the target for a sample with a mean COI of (b) (4) *; [B.] Precision result used in comparison to the target for a sample with a mean COI of* (b) (4) *.*

Elecsys HBsAg II Auto Confirm

Reproducibility of the Elecsys HBsAg II Auto Confirm was evaluated at three sites, with (b) (4) , using three lots of Elecsys HBsAg II Auto Confirm assay and one lot of PreciControl HBsAg II Auto Confirm 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 HBsAg II kits yielding 270 test results per panel member (2 runs/day x 5 days x 3 replicates/concentration x 3 sites x 3 reagent lots). The member panel included:

- (b) (4) low HBsAg reactive sample at the target (b) (4) S/CO
- (b) (4) high HBsAg reactive sample at target (b) (4) S/CO

Additionally, two lots of PreciControls were tested as samples:

- PreciControl HBSAG2 B at target level (b) (4) S/CO

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys HBsAg II Auto Confirm assay. The results of the reproducibility panel and control testing demonstrate that Elecsys HBsAg II Auto Confirm assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 13 - 15)

Table 13. Overall repeatability and reproducibility for control reaction Elecsys HBsAg II Auto Confirm

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Intermediate Precision		Between-Site		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	1.63	270	0.059	3.63[B]	0.010	0.589	0.018	1.10	0.063	3.83[B]	0.020	1.25	0.088	5.38	0.110	6.72[B]
HSP 02	4.86	270	0.129	2.66[B]	0.058	1.20	0.055	1.14	0.152	3.13[B]	0.110	2.27	0.313	6.45	0.365	7.52[B]
PreciControl HBSAGCB	3.63	270	0.100	2.74[B]	0.065	1.78	0.082	2.25	0.144	3.97[B]	0.000	0.000	0.343	9.44	0.372	10.2[B]

[B.] Precision result used in comparison to the target for a sample with a mean COI of ≥0.81.

Table 14. Overall repeatability and reproducibility for confirmation result Elecsys HBsAg II Auto Confirm

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Intermediate Precision		Between-Site		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	0.301	270	0.028	9.43	0.014	4.68	0.010	3.21	0.033	11.0	0.002	0.780	0.026	8.52	0.042	13.9
HSP 02	0.710	270	0.034	4.76	0.000	0.000	0.011	1.56	0.036	5.01	0.003	0.457	0.030	4.26	0.047	6.59
PreciControl HBSAGCB	0.414	270	0.036	8.77	0.010	2.45	0.004	0.960	1.038	9.16	0.006	1.55	0.022	5.23	0.044	10.7

Table 15. Overall repeatability and reproducibility for confirmation result (%) Elecsys HBsAg II Auto Confirm

Sample	Mean	N	Repeatability		Between-Run		Between-Day		Intermediate Precision		Between-Site		Between-Lot		Reproducibility	
			SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]	SD	CV [%]
HSP 01	18.6	270	1.88	10.1[B]	0.756	4.07	0.477	2.57[B]	2.08	11.2	0.377	2.03	2.49	13.4	3.26	17.6[B]
HSP 02	14.7	270	0.768	5.22[B]	0.000	0.000	0.251	1.71[B]	0.809	5.50	0.226	1.53	1.63	11.1	1.83	12.4[B]
PreciControl HBSAGCB	11.5	270	0.987	8.56[B]	0.308	2.67	0.090	0.78[B]	1.04	9.00	0.202	1.75	1.78	15.4	2.07	18.0[B]

[B.] *Precision result used in comparison to the target for a sample with a mean COI of ≥0.81.*

e) BIMO – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed for three domestic clinical study sites participating in the conduct of study Protocol RD005615. The inspections did not reveal substantive findings that impact the data submitted in this BLA.

f) Pediatrics

N/A

g) Other Special Populations

N/A

7. Advisory Committee Meeting

N/A

8. Other Relevant Regulatory Issues

None.

9. Labeling

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Package Inserts and Package and Container labels on December 11, 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 and therefore the Review Committee recommends licensure of the Elecsys HBsAg II and Elecsys HBsAg II Auto Confirm assays.

b) Risk/ Benefit Assessment

The risk/benefit analysis demonstrates that the benefit of the Elecsys HBsAg II and the Elecsys HBsAg II Auto Confirm assays outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies with the Elecsys HBsAg II assay and Elecsys HBsAg II Auto Confirm assay demonstrate

a sensitivity of 100% (95% CI of 99.34% – 100.00%), indicating a low probability of a false negative result. Among 14,284 blood and plasmapheresis donors tested with the Elecsys HBsAg II, the assay specificity of 99.96% (95% CI of 99.92 – 99.99%) in clinical trials suggests a low probability of a false positive result.

c) Recommendation for Post-Marketing Activities

No post-marketing activities have been proposed for this application.