Summary Basis for Regulatory Action

Date:	February 26, 2024
From:	Kavita Singh, Ph.D., Chair of the Review Committee
BLA/ STN#:	125804/0
Applicant Name:	Roche Diagnostic Solutions 9115 Hague Road; Indianapolis, IN 46256
Date of Submission:	May 1, 2023
MDUFA Goal Date:	February 29, 2024
Proprietary Name:	Elecsys Anti-HBc II PreciControl Anti-HBc II PreciControl Release Anti-HBc II

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

Intended Use/Indications for Use:
Elecsys Anti-HBc II is an in vitro immunoassay for the qualitative detection of antibodies to hepatitis B core antigen (anti-HBc) in human serum and plasma. Elecsys Anti HBc II is intended to screen individual human donors, including volunteer donors of whole blood and blood components. The assay is also intended to be used to screen organ, tissue, and cell donors, when donor samples are obtained while the donor's heart is still beating. It is not intended for use on cord blood specimens.
The **e**lectro**c**hemi**l**uminescence **i**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, MD, PhD; Director, Office of Blood Research and Review

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

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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*	Krishna Devadas	12/12/2023
• *Non-Clinical*	David McGivern Caren Chancey	01/04/2024 02/05/2024
Statistical Review • *Clinical and Non-Clinical (OBPV/DB/DNCE)*	Linye Song	11/08/2023
CMC Review • *CMC (OBRR/DETTD)*	Viswanath Ragupathy Mohan Haleyurgirisetty	12/27/2023 01/11/2024
• *Facilities Review (OCBQ/DMPQ)*	Prajakta Varadkar	02/07/2024
• *Microbiology Review (OCBQ/DBSQC)*	Simleen Kaur	11/6/2023
• Establishment Inspection Report(s) (*OCBQ/DMPQ*)	Prajakta Varadkar	06/22/2023
Labeling Review(s) • *OBRR* • *APLB (OCBQ/APLB)*	Kavita Singh Sadhna Khatri	10/11/2023 12/15/2023
Lot Release Protocols/Testing Plans/Testing Panel (*OCBQ/DBSQC*)	George Kastanis Ishrat Sultana	02/13/2024 01/23/2024
Bioresearch Monitoring Review (*OCBQ/BIMO*)	Kanaeko Ravenell Yakubu Wangabi	01/12/2024
Software and Instrumentation (*OBRR/DETTD*)	Rana Nagarkatti	01/25/2024
Other living donor (OTP/DHT)	Hanh Khuu	09/11/2023

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1. Introduction

The Elecsys Anti-HBc II assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4), Germany. This biologics license application (BLA) for Elecsys Anti-HBc II assay from Roche Diagnostics Solutions, 9115 Hague Road Indianapolis, IN 46250, USA was received on May 1, 2022. The application was assigned the number STN 125804/0 and granted a standard 10-month review status with a goal date of February 29, 2023. The application was filed June 5, 2023, and the mid-cycle meeting took place on October 18, 2023.

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

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

Date	Action	Amendment to BL125804
May 1, 2023	BLA application receipt	/0
May 3, 2023	Acknowledgement Letter	
May 09, 2023	RD submitted an Amendment for updating the serology controller software from version 1.0.3 to version 1.1.	/0/01
May 17, 2023	Information Request for updated 356 Form with correct FEI and DUNS registrations.	
May 18, 2023	Response to IR dated May 17, 2023: RD submitted amendment to correct the FDA form 356h site information for the FEI and DUNS registrations.	/0/02, 0/05
May 24, 2023	Information Request for Lot Release Protocol Template	
May 30, 2023	Response to IR dated May 24, 2023: RD submitted a Lot Release Protocol Template	/0/03

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Date	Action	Amendment to BL125804
May 31, 2023	Response to IR dated May 24, 2023: RD submitted CORRECTED Lot Release Protocol Template	/0/04
June 5, 2023	Filing Notification Letter	
June 22, 2023	Facility Inspection Waiver	
August 4, 2023	Information Request for Non-Clinical data (Precision, LoB/LoD for Serum and Plasma, Seroconversion Sensitivity, Drug Interference, Transport Stability and PreciControl Shelf-life Stability)	
August 11, 2023	Information Request for Antimicrobial Effectiveness Testing (AET) and Bioburden	
August 18, 2023	Response to IR dated August 4, 2023: RD provided the requested Non-Clinical data	/0/06
August 18, 2023	Response to IR dated August 11, 2023: RD provided the requested information for Bioburden and AET testing	/0/07
August 24, 2023	Information Request for Non-Clinical (Cross-reactivity, Transport Stability) and Clinical data (Sensitivity testing for serum and plasma)	
August 31, 2023	Response to IR dated August 24, 2023: RD provided the Non-Clinical and Clinical data	/0/08
September 27, 2023	Information Request for the shipping address for the blinded panel	
September 27, 2023	Response to IR dated September 27, 2023: RD provided the shipping address to send the blinded panels	/0/09
October 3, 2023	Information Request for Non-Clinical data (On-Clot Stability)	
October 5, 2023	Response to IR dated October 3, 2023: RD provided the Non-Clinical data	/0/10

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Date	Action	Amendment to BL125804
October 10, 2023	Information Request for serum/plasma comparison study	
October 12, 2023	Response to IR dated October 10, 2023: RD provided the serum/plasma comparison data	/0/11
October 31, 2023	Response to IR dated Aug 11, 2023: RD provided the final bioburden verification report	/0/12
November 8, 2023	Information Request for correct Environmental Impact Analysis	
November 8, 2023	Response to IR dated November 8, 2023: RD provided the correct Environmental Impact Analysis	/0/13
December 4, 2023	RD submitted an Amendment with completed Lot Release Protocols	/0/14, /0/17
January 24, 2024	Response to IR dated January 22, 2024: RD provided the Lot Release Protocol and (b) (4) serology Contact Info Letter	/0/15, /0/16
February 8, 2024	Information Request for labeling edits to harmonize with other Elecsys assays	
February 12, 2024	RD response to IR dated February 8, 2024, on Elecsys Anti-HBc II labeling	/0/18

2. Background

The Elecsys Anti-HBc II is a qualitative serologic, three-step assay, that uses the competitive test format for the detection of hepatitis B core antigen (HBcAg) in human serum and plasma. The assay involves three incubation steps: in the first incubation step, the sample is pretreated with the reducing agent; in the second step, HBcAg is added, forming complexes with Anti-HBc antibodies in the sample; and in the third step, biotinylated antibodies and ruthenium complex-labeled antibodies specific for HBcAg are added together with streptavidin-coated microparticles. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin. The immunoassay 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 of the cutoff value, previously obtained by calibration. The result of a sample measurement is given either as reactive or non-reactive, as well as in the form of a signal/cutoff (S/CO). Samples with a S/CO > 1.00 are considered non-reactive for HBc specific antibodies and do not need further testing. Samples with a S/CO ≤ 1.00 are considered initially reactive on the Elecsys Anti-HBc II assay. All initially reactive samples are automatically retested in duplicate using the Elecsys Anti-HBc II assay. Validation of all results is based on test result batches that are concluded by successful release control measurements.

The **cobas pro** serology solution is intended for use only with licensed blood screening assays by U.S. blood banks and plasma fractionators. It is intended for use only by personnel who are trained in its operation. Detailed device description is provided in the CMC and Software and Instrumentation sections below.

3. Chemistry Manufacturing and Controls (CMC)

The manufacturing of the Elecsys Anti-HBc II assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Elecsys Anti-HBc II 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 Anti-HBc II kit (List Number 09014926162) consists of 10 reagent cassettes (**cobas e** packs) each containing the components M, R0, R1, and R2, and two identical calibrator packs, each containing the components AHBC2B Cal1 and AHBC2B Cal2. The kit components are listed below:

- Component M: Streptavidin-coated microparticles for capturing biotin-complex
- Component R0: Buffered reducing agent

- Components R1 and R2: R1 (Recombinant hepatitis B core antigen) and R2 (biotinylated-monoclonal anti-HBc antibody and ruthenylated-monoclonal anti-HBc antibody) reactive component as Ab-Ag-complex builder
- AHBC2B Cal1: Non-reactive calibrator 1, human serum negative for anti-HBc antibodies
- AHBC2B Cal2: Reactive calibrator 2, human serum positive for anti-HBc antibodies

PreciControl Anti-HBc II (List Number 04927931162), supplied separately, is used for quality control of Elecsys Anti-HBc II. The control kit consists of the following components:

- PC AHBC1 B: Negative control, human serum non-reactive for anti-HBc antibodies
- PC AHBC2 B: Positive control, human serum reactive for anti-HBc antibodies

PreciControl Release Anti-HBc II (PC AHBCR; List Number 09367039190), identical to PC AHBC2 B, supplied separately, is used as a release control, and consists of the human serum reactive for anti-HBc 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
- PreClean II M (List Number 06908853190): Wash solution
- ISE Cleaning solution/Elecsys SysClean (11298500160): 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
- Reservoir cup (List Number 07485409001): Cups to supply ProCell II M and CleanCell M solutions

b) Testing Specifications

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

c) CBER Lot Release

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

d) Facilities Review/Inspection

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

Table 3. Manufacturing facilities for Elecsys Anti-HBc II

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification /Results
Roche Diagnostics GmbH (b) (4) *Manufacturing of Elecsys kit components and Control reagents. Release testing of final device (assay).*	(b) (4)	(b) (4)	Waived	CDER Pre-License Inspection (b) (4); VAI ORA Post-Market Approval Inspection (b) (4); NAI
Roche Diagnostics GmbH Sandhofer Strasse 116, 68305 Mannheim, Germany *Labeling and final assembly of Elecsys HTLV-I/II kit and PreciControl. Manufacturing, labeling, and packaging of system reagents.*	3002806559	315028860	Waived	MRA Inspection Review by ORA/OPQO (b) (3); VAI ORA For-Cause Inspection August 2019; VAI ORA Post-Market Approval Inspection April 2018; NAI

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CDER – Center for Drug Evaluation and Research; 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 in (b) (4) at Roche Diagnostics GmbH, (b) (4) Germany for the BLA (b) (4) for (b) (4) drug substance and BLA (b) (4) for (b) (4) drug substance manufacturing and testing. The inspection covered the Warehouse and the Quality Control Laboratories associated with the subject BLA. All FDA Form-483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

Office of Regulatory Affairs (ORA) performed a post-market approval inspection in (b) (4) at Roche Diagnostics GmbH, (b) (4) Germany. 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 Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations performed a review of a GMP inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (3) 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 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

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

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

4. Software and Instrumentation

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

a) Versioning

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

b) Device Description

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

The **cobas pro** automates electrochemiluminescence immunoassay test processing, result interpretation, and data management functions for screening of donations of whole blood and blood components using plasma or serum samples. For blood donor screening, each **cobas pro** integrated solutions configuration consists of up to four **cobas e** 801 analytical units. The **cobas e** 801 is a fully automated immunoassay analyzer intended to perform high throughput routine and priority testing (300 tests/hour) while allowing continuous access and automated retesting. The **cobas e** flow assay specific software modules, assay specific parameters included in the Application Code Numbers (ACN) and in the

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

c) Risk Management

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

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

encryption, and configuration management, among others. The applicant concluded the overall residual risk of the **cobas pro** serology solution is acceptable. This assessment appears to be supported by the evidence provided.

d) Unresolved Anomalies

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

e) Testing

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

f) Development Management

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

Review Note: As agreed to in BQ170139/1, Roche submitted a software update for the Serology Controller software from version 1.0.3 to 1.1.0 in Amendment 1 received on May 9, 2023. This software update affects all Elecsys submission under review. The update includes automation of the onboard stability and usage tracking of calibrator/control material, automation of the HBsAg Auto Confirm assay (not reviewed in the current BLA as Elecsys Anti-HBc II assay is not impacted by this change), 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 Anti-HBc II BLA is not impacted by this update.

5. Analytical Studies

The analytical studies were conducted in compliance with 21 CFR Part 58 (Good

Laboratory Practices or GLPs), as applicable and were performed at Roche Diagnostics GmbH, (b) (4) Germany.

a) Precision Studies

Precision of the Elecsys Anti HBc II assay was evaluated at one site with (b) (4) , one lot of Elecsys Anti-HBc II assay and one lot of PreciControl Anti-HBc II. The samples were tested over 21 days, with one run per day, using four replicates, yielding n=84 measurements per sample. The member panel included:

- Two Anti-HBc antibody negative specimen at target (b) (4) S/CO
- Two Anti-HBc antibody high-negative specimens at target (b) (4) S/CO
- One Anti-HBc antibody low positive sample at target (b) (4) S/CO
- One Anti-HBc antibody positive sample at target (b) (4) S/CO
- PreciControl AHBC1 B Level 1 at target (b) (4) S/CO
- PreciControl AHBC2 B Level 2 at target (b) (4) S/CO

Table 4: Intermediate (Within-Laboratory) Precision for Elecsys Anti-HBc II

Sample	Mean S/CO	N	Repeatability SD [S/CO]	Repeatability CV [%]	Within-Laboratory Precision SD [S/CO]	Within-Laboratory Precision CV [%]
HSP 1	2.13	84	0.031	1.2	0.037	1.7
HSP 2	1.10	84	0.018	1.7	0.030	2.8
HSP 3	1.01	84	0.014	1.4	0.028	2.8
HSP 4	0.004	84	0.000	1.2	0.000	2.2
HSP 5	0.92	84	0.017	1.9	0.028	3.1
HSP 6	1.48	84	0.024	1.6	0.032	2.2
PC AHBC1 B	2.41	84	0.028	1.2	0.043	1.8
PC AHBC2 B	0.64	84	0.008	1.3	0.017	2.8

HSP=Human Specimens; PC= PreciControls; N = number of replicates; CV = coefficient of variation expressed as a percentage (CVs are not meaningful when S/CO approaches zero); SD = standard deviation; S/CO = signal/cut-off; PC AHBC1 B = Negative control, human serum non-reactive for Anti-HBc antibodies; PC AHBC2 B = Positive control, human serum reactive for Anti-HBc antibodies.

The data demonstrate acceptable within-laboratory precision of the Elecsys Anti-HBc II assay.

b) Limit of Detection

(b) (4)

c) Analytical Sensitivity

Analytical sensitivity of Elecsys Anti-HBc II assay was evaluated using the WHO First International Standard for anti-Hepatitis B core antigen (anti-HBc), plasma, human (NIBSC code number: 95/522). A six-dilution series of WHO International Standard 95/522 were prepared between (b) (4) IU/ml in Anti-HBc negative serum and tested in duplicates with (b) (4), at (b) (4), with (b) (4). Sensitivity was calculated using the mean of both duplicate measurements tested by reading off the concentration at the cutoff of 1.0 from the Anti-HBc reference standard curve. The data demonstrate acceptable performance with respect to the known WHO standard 95/522 concentration of ≤ 0.8 IU/mL, as the candidate assay result for NIBSC code 95/522 was determined to be 0.451 IU/mL.

d) Seroconversion Sensitivity

The seroconversion sensitivity of the Elecsys Anti-HBc II assay was compared to the sensitivity of FDA-licensed assays. For determination of seroconversion sensitivity, a total of 10 seroconversion panels from three vendors were tested with a total of 159 panel members with Elecsys Anti-HBc II and compared to three different comparator assays. There was one discordant panel member in each of three panels, where the Elecsys Anti-HBc II assay detected seroconversion one bleed later than the comparator assay. The summary of the results obtained from 10 commercially available seroconversion panels is in the following Table 5.

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Table 5: Elecsys Anti-HBc II Assay Reactivity in Seroconversion Panels

Panel ID	Comparator Total Negative Bleeds	Comparator Total Positive Bleeds	Elecsys Anti-HBc II Total Negative Bleeds	Elecsys Anti-HBc II Total Positive Bleeds	Differences in bleeds Elecsys Anti-HBc II vs Comparator*
Panel 1 SCP-HBV-001	4	16	4	16	0
Panel2 SCP-HBV-002	6	14	7	13	+1
Panel3 SCP-HBV-004	13	17	13	17	0
Panel 4 PHM941	4	3	4	3	0
Panel 5 HBV-6278	9	2	10	1	+1
Panel 6 HBV-6281	8	4	8	4	0
Panel 7 HBV-9093	9	22	10	21	+1
Panel 8 PHM933	4	1	4	1	0
Panel 9 PHM934	5	1	5	1	0
Panel 10 PHM935A	10	7	10	7	0

* -1 = Elecsys Anti-HBc II one bleed earlier, 0 = equal, +1 = Elecsys Anti-HBc II one bleed later

e) Endogenous Interferences (Spiked)

Assay performance was evaluated in samples with high levels of spiked interferents (hemoglobin, lipemia, bilirubin, rheumatoid factor, and human serum albumin for total protein) using (b) (4)

(b) (4) . The data demonstrate acceptable performance of the assay for both nonreactive and reactive samples, supporting the use of the Elecsys Anti-HBc II with donor specimens containing up to (b) (4) mg/dL of hemoglobin, 2000 mg/dL lipid, (b) (4) mg/dL bilirubin, (b) (4) rheumatic factor and 7.0 g/dL of total protein. In addition, (b) (4) tested for interference was (b) (4) . No interference was observed up to a biotin concentration of (b) (4) ng/mL using the Elecsys Anti-HBc II assay.

f) 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 was evaluated. A total of (b) (4) Anti-HBc negative serum and plasma 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)), (b) (4) of triglycerides (range tested (b) (4)), (b) (4) of total bilirubin (range tested (b) (4)), (b) (4) of total protein ((b) (4)), and (b) (4) of rheumatoid factor (range tested (b) (4)).

g) Cross Reaction/Analytical Specificity

Analytical specificity of the Elecsys Anti-HBc II assay was evaluated by testing specimens with conditions or disease states unrelated to HBc infection. A total of 293 samples containing potentially interfering factors listed below were spiked individually with Anti-HBc antibodies ((b) (4) samples for each disease state or condition), and the effect of potentially interfering factors was tested. The following specimens were used:

- Containing antibodies against HIV, HAV (b) (4) , HBV (acute), HCV, Rubella (b) (4) , HSV (b) (4) , EBV (b) (4) , HEV, HDV, HTLV-I/II, Parvo B19, VZV, (b) (4)
- Containing autoantibodies (ANA), Heterophilic antibodies (HAMA), elevated titers of rheumatoid factor (RF)
- Positive for antibodies against *Candida albicans*, *Chlamydia*, *E. coli*, *Plasmodium*, and *Treponema pallidum* (Syphilis)
- After vaccination against influenza
- From persons with (b) (4)
- From pregnant women and multiparous pregnancies

The obtained data demonstrate acceptable performance of the assay and indicate that the presence of potentially interfering substances or medical conditions included in the study has no effect on the detection of Anti-HBc antibodies. There

was no significant effect on background signals in negative specimens (neat specimens).

h) Drug interference

Potential interference with the Elecsys Anti-HBc II assay from common therapeutic drugs was tested using Anti-HBC II negative and positive samples spiked individually with the following drugs: (b) (4) . No interference with Elecsys Anti-HBc II assay was detected from the drugs tested at concentrations of at least (b) (4) times the highest blood concentration detected under therapeutic treatment ((b) (4)).

i) Serum and Plasma Comparison

The impact of anticoagulants on the performance of the Elecsys Anti-HBc II assay was evaluated using (b) (4) ((b) (4) for citrate phosphate dextrose [CPD]) matched serum and plasma specimens collected from individual donors. Reactive samples and near cut-off non-reactive samples were contrived by collecting (b) (4) ((b) (4) CPD) individual non-reactive donor samples and (b) (4) A total of (b) (4) ((b) (4) for CPD) 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 CPD was compared to the performance demonstrated when testing serum specimens. In addition, the suitability of different blood collection tubes was evaluated by testing samples collected with serum-, K2-EDTA- and lithium heparin- separation tubes. The data demonstrate acceptable performance of the assay with specimens collected in the anticoagulants and tube types listed above supporting the use of specimens collected in these anticoagulants and tube types.

j) Specimen Storage

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

The data demonstrate acceptable performance of the assay supporting the use of serum and plasma specimens that were stored at approximately 15 to 30°C for up to 7 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 3 months, and up to (b) (4) freeze/thaw cycles. These data support the storage claims in the package insert.

k) Specimen Processing

Assay performance with centrifuged liquid (never frozen) and previously frozen specimens was evaluated using (b) (4) serum specimens — Anti-HBc II antibody negative (n=(b) (4)), spiked with Anti-HBc antibody (n=(b) (4)) low positive, and with Anti-HBc II antibody high positive (n=(b) (4)) — compared to the uncentrifuged, homogenized reference. The target concentrations ranged from (b) (4) S/CO. The data demonstrate acceptable performance of the assay supporting the use of the assay with non-frozen and previously frozen serum specimens when centrifuged for 10 to 15 minutes at 2000 to 4000 RCF (relative centrifugal force = x g).

l) On-clot Specimen Processing

Assay performance with serum and plasma (K_2-EDTA, Sodium Citrate, and Lithium Heparin) specimens after storage on-clot was evaluated using (b) (4) specimens across all specimen types — Anti-HBc II antibody negative (n=(b) (4)) and Anti-HBc II antibody positive (n=(b) (4)) and compared to specimens stored at unstressed conditions. The target concentrations ranged from (b) (4) S/CO. The data demonstrate acceptable performance of the assay supporting the use of the assay with samples stored on-clot for 7 days at 15 to 30°C and 14 days at 2 to 8°C.

m) Kit Lot Calibration and On-Board Calibration Stability

Calibration of the Elecsys Anti-HBc II assay must be performed once per reagent lot using AHBC2B Cal1, AHBC2B Cal2 and fresh reagent. Lot calibration stability was validated using Elecsys Anti-HBc II kit of the same lot stored at 2 to 8°C up to (b) (4) weeks using the initial calibration. A total of (b) (4) serum specimens — Anti-HBc II antibody negative (n=(b) (4)), spiked (n=(b) (4)) at analyte level range (b) (4) S/CO along with (b) (4) PreciControls —were tested in (b) (4) and compared to unstressed reagents of the same lot measured using the initial calibration. The data demonstrate acceptable performance of the assay supporting a Lot Calibration stability of up to 12 weeks. In addition, On-Board calibration stability was validated using (b) (4) serum specimens — Anti-HBc II antibody negative (n=(b) (4)), spiked (n=(b) (4)) at analyte level range (b) (4) S/CO along with (b) (4) PreciControls — were tested using Elecsys Anti-HBc II kit components in (b) (4) on the opening day (unstressed) and for (b) (4) days stored under on-board conditions on a **cobas e** 801 analyzer. Acceptable performance was observed, supporting the On-Board stability of up to 28 days using the initial calibration.

Summary Basis for Regulatory Action

n) Reagent Stability Studies

Reagent real time stability was validated using (b) (4) Elecsys Anti-HBc II kit lots stored at 2 to 8°C up to (b) (4) months compared to t = 0 months. A total of (b) (4) serum specimens –Anti-HBc II antibody negative (n=(b) (4)), and Anti-HBc II antibody low and high positive (n=(b) (4)) at the reactivity range (b) (4) S/CO along with two 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 (b) (4) months at 2 to 8°C. A sample panel of (b) (4) serum specimens at the reactivity range (b) (4) S/CO was utilized to evaluate on-board stability of the Elecsys Anti-HBc II kit components when stored at (b) (4) for (b) (4) weeks. Transport stability was evaluated at (b) (4) for (b) (4) when compared to unstressed kits stored at 2 to 8°C to evaluate stability during shipping. Acceptable performance was observed, supporting an on-board stability claim of up to 16 weeks at (b) (4) and a transportation claim of up to (b) (4) at (b) (4).

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

Assay performance with specimens, calibrators, and controls directly after storage at 2 to 8°C was evaluated using (b) (4) serum specimens — Anti-HBc II antibody negative (n=(b) (4)), and Anti-HBc II antibody positive (n=(b) (4)) — and compared with samples that were equilibrated at (b) (4). The target concentrations obtained ranged from (b) (4) S/CO. The data demonstrate acceptable performance of the assay supporting the use of specimens and kit components without first equilibrating for (b) (4).

p) Calibrator Stability

Calibrators are supplied ready-for-use in vials compatible with the system. Stability of calibrators was evaluated by measuring them in (b) (4) after storage under various conditions. The data demonstrate acceptable performance of calibrators supporting stability claims of storage for 5 hours at 20°C to 25°C, and up to 16 weeks at 2 to 8°C.

q) PreciControl Stability

The PreciControl Anti-HBc II is supplied as ready-for-use in vials used for monitoring the accuracy of the Elecsys Anti-HBc II assay. Stability of PreciControl (PC) AHBC1B and PC AHBC2B was evaluated after storage under various conditions compared to t = 0 by (b) (4) measurements. The data demonstrate acceptable performance of PreciControls supporting stability claims of storage for up to 5 hours at 20 to 25°C, up to 21 months at 2 to 8°C, and up to (b) (4) at 2 to 8°C after first opening. Multiple-use stability data were acceptable for up to (b) (4) quality control procedures when stored at 20 to 25°C.

r) Within-Assay Carryover

Sample to sample carryover was evaluated using a panel of (b) (4) high positive and (b) (4) negative samples run (b) (4) times on (b) (4) **cobas e** 801 analyzers. HBsAg II assay was used as a surrogate because high concentration spiked samples ((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 HBsAg II assay LoD of (b) (4) . No sample-to-sample carryover was detected.

s) Cadaveric Studies

No cadaveric claims were sought by sponsor in this BLA.

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

t) Microbial Challenge

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

6. Clinical Studies

Clinical studies were conducted to evaluate assay sensitivity, specificity, and reproducibility to demonstrate performance in the intended use population of the Elecsys Anti-HBc II assay. Testing was performed at three blood donor testing laboratories and confirmatory testing was conducted at one additional site. Three lots of the Elecsys Anti-HBc II Reagent Kit, and one lot each of the PreciControl Anti-HBc II, and the PreciControl Anti-HBc II Release Control Kit were used for the studies at each of the testing sites.

The results from Elecsys Anti-HBc II specimens were compared against those of an FDA-licensed comparator assay. In the event of discordant results, donor specimen final status was determined by a testing a follow-up sample. The follow-up specimen status was determined by supplemental test results, and if inconclusive, an expert panel resolved the initial inconclusive results to Positive or Negative. An initial status of inconclusive was maintained if a follow-up sample was not obtained.

a) Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Elecsys Anti-HBc II assay on the **cobas e** 801 analyzer and using an FDA-licensed comparator assay by testing a total of 7667 specimens. All donors enrolled were evaluated and no donation was excluded.

Summary Basis for Regulatory Action

Of the 7667 specimens tested, 3763 fresh serum and 3904 fresh plasma samples from voluntary blood donors were tested at three (b) (4) sites using an FDA-licensed comparator. The specimens were collected from 6803 repeat donors and 864 first time donors. All initial reactive samples were repeat reactive; therefore, the initial and repeat reactive rates for serum specimens were 0.21 % (8/3763) and for plasma specimens were 0.13% (5/3904). Overall, the initial and repeat reactive rates for the Elecsys Anti-HBc II assay were 0.017% (13/7667).

A total of 13 donor samples were repeatedly reactive using the Elecsys Anti-HBc II assay and 15 donor samples were repeatedly reactive on the comparator assay, 10 of which were reactive using both assays and were confirmed as true positive samples based on algorithm testing. There were eight samples where the Elecsys and comparator results were discordant: three of the discordant samples were repeatedly reactive on the Elecsys assay and were non-reactive on the comparator assay, and five were repeatedly reactive on the comparator assay and were non-reactive on the Elecsys assay. The final specimen status of these eight samples was determined to be Negative based on the additional supplemental testing using FDA-licensed assays and with the resolution of inconclusive results through an expert panel. Samples with a final Anti-HBc status of Positive were not included in the specificity calculation.

The specificity of the Elecsys Anti-HBc II assay relative to the final anti-HBc antibody status in whole blood donors was calculated to be 99.96% (7654/7657) with a 95% Confidence Interval (CI) of 99.88% to 99.99% as presented in Table 6.

Table 6: Elecsys Anti-HBc II Clinical Study. Specificity of the Elecsys Anti-HBc II Assay in Donors

Specimen Category	N	IR (% of Total)	RR (% of Total)	Number RR that were Positive by Supplemental Testing (% of RR)	Specificity (%) [a] (95% CI)
Volunteer Blood Donors – Serum	3763	8 (0.21)	8 (0.21)	6 (0.16)	99.95% 3755/3757 (99.81 – 99.99%)
Volunteer Blood Donors – Plasma	3904	5 (0.13)	5 (0.13)	4 (0.10)	99.97% 3899/3900 (99.85 – 100.00 %)
Total Volunteer Blood Donors	**7667**	**13 (0.17)**	**13 (0.17)**	**10 (0.13)**	**99.96% 7654/7657 (99.88 – 99.99%)**

N = Number tested; IR = initially reactive; RR = repeatedly reactive; CI = confidence interval.
[a] Based on supplemental test results for the 3 repeatedly reactive specimens (2 serum and 1 plasma).

b) Clinical Sensitivity

Elecsys Anti-HBc II assay sensitivity was established by analyzing test results for 898 positive specimens from four sensitivity cohorts and compared to the results of the licensed comparator assay. Testing was performed at three clinical sites. Elecsys Anti-HBc II repeatedly reactive specimens were confirmed with supplemental testing using FDA-licensed assays.

Out of 898 tested specimens, 308 were serum and 590 were plasma. The sensitivity for serum was calculated to be 99.35% (306/308) with a 95% confidence interval of 97.66% to 99.82% and sensitivity for plasma was calculated to be 100% (590/590) with a 95% confidence interval of 99.35% to 100%. Two specimens that were non-reactive on the Elecsys assay and repeatedly reactive on the comparator assay were positive by supplemental testing. Overall sensitivity was determined to be 99.78% (896/898) with a 95% confidence interval of 99.19% to 99.94% as presented in Table 7.

Table 7: Elecsys Anti-HBc II Clinical Study. Overall Sensitivity Summary

Specimen Category	N	Number Positive	Number RR (% of Tested)	Number RR that were Positive by Supplemental Testing (% of RR)	Sensitivity (%) (95% CI)
Acute HBV	45	45	45 (100)	45 (100)	100% 45/45 (92.13 – 100.00%)
Anti HBc Positive	483	481	481 (99.59)	481 (100)	95.59% 481/483 (98.50 – 99.89%)
Chronic HBV	113	113	113 (100)	113 (100)	100% 113/113 (96.71 – 100.00%)
HBV Recovered	257	257	257 (100.00)	257 (100)	100.00% 257/257 (98.53% - 100.00%)
Total	**898**	**896**	**896 (100)**	**896 (100)**	**99.78% 896/898* (99.19 – 99.94%)**

N = number tested; RR = Repeatedly Reactive. * Two Elecsys Anti-HBc II non-reactive specimens were positive by supplemental testing.

c) Reactivity in Increased Risk Populations and Endemic Areas

Elecsys Anti-HBc II performance in an untested increased risk for hepatitis B infection population was evaluated using a total of 409 specimens. A total of 100 specimens were determined to be repeatedly reactive with a specimen status of positive based on the algorithm. These specimens had repeatedly reactive results on the Elecsys Anti-HBc II and the comparator assays. A total of 308 specimens were interpreted as negative: 307 were Elecsys Anti-HBc II non-reactive with a negative status and one sample was Elecsys Anti-HBc II repeatedly reactive result with a negative status based on the algorithm and the additional supplemental testing. One unresolved specimen was interpreted as inconclusive with repeatedly reactive Elecsys Anti-HBc II results. Sensitivity was not analyzed in this cohort and only the comparative results are presented in Table 8.

Table 8. Elecsys Anti-HBc II Testing in Individuals at Increased Risk for Hepatitis Infection

Assay Result	Final Specimen Status Positive [n]	Final Specimen Status inconclusive [n]	Final Specimen Status Negative [n]	Sum [n]
Repeatedly reactive	100	1	1	102
Non-reactive	0	0	307	307
Total	**100**	**1**	**308**	**409**

d) Reproducibility Studies

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

- One low Anti-HBc II antibody sample at the target S/CO 0.596
- One high Anti-HBc II antibody sample at target S/CO 0.006

Additionally, three lots of PreciControls were tested as samples:

- PreciControl AHBC1 B at S/CO 2.33
- PreciControl AHBC2 B at target S/CO 0.581

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys Anti-HBc II assay. The

results of the reproducibility panel and control testing demonstrate that the Elecsys Anti-HBc II assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 9**.**

Table 9: Overall Repeatability and Reproducibility for Elecsys Anti-HBc II

a. Repeatability, Between Run and Between Day Precision:

Sample	Mean S/CO	N	Repeatability SD	Repeatability CV [%]	Between Run SD	Between Run CV [%]	Between Day SD	Between Day CV [%]
HSP 14	0.596	270	0.011	1.91	0.010	1.63	0.010	1.62
HSP 15	0.006	270	0.000	1.95	0.000	0.391	0.000	0.559
PC AHBC1 B	2.33	270	0.054	2.34	0.000	0.000	0.021	0.910
PC AHBC2 B	0.581	270	0.006	1.06	0.006	1.08	0.006	1.02

HSP 14 = low anti-HBc II antibody human specimen, HSP 15 = high anti-HBc II antibody human specimen; PC = PreciControls; N = number of replicates; CV = coefficient of variation expressed as a percentage (CVs are not meaningful when S/CO approaches zero); SD = standard deviation

b. Intermediate Precision and Between Site Reproducibility:

Sample	Mean S/CO	N	Intermediate Precision SD	Intermediate Precision CV [%]	Between Site SD	Between Site CV [%]
HSP 14	0.596	270	0.018	2.99	0.005	0.816
HSP 15	0.006	270	0.000	2.07	0.000	0.993
PC AHBC1 B	2.33	270	0.058	2.51	0.027	1.14
PC AHBC2 B	0.581	270	0.011	1.83	0.008	1.33

c. Between Lot and Overall Reproducibility:

Sample	Mean S/CO	N	Between Lot SD	Between Lot CV [%]	Reproducibility SD	Reproducibility CV [%]
HSP 14	0.596	270	0.039	6.52	0.043	7.22
HSP 15	0.006	270	0.000	4.18	0.000	4.77
PC AHBC1 B	2.33	270	0.014	0.589	0.066	2.82
PC AHBC2 B	0.581	270	0.019	3.19	0.023	3.91

e) BIMO – Clinical/Statistical/Pharmacovigilance

A BIMO inspection assignment was issued for three domestic sites participating in the study conduct of Protocol RD005615 in support of this BLA. The inspections

did not reveal significant problems impacting the data submitted in the application.

f) Pediatrics

N/A

g) Other Special Populations

N/A

7. Advisory Committee Meeting

N/A

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 December 15, 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 Anti-HBc II assay.

b) Risk/Benefit Assessment

The risk/benefit analysis demonstrates that the benefit of the Elecsys Anti-HBc II assay outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 99.78% (95% CI of 99.19 – 99.94%), indicating a low probability of a false negative result. Among 7657 blood donors tested with the Elecsys Anti-HBc II assay, the assay specificity of 99.96% (95% CI of 99.88 – 99.99%) in clinical trials suggests a low probability of a false positive result.

c) Recommendation for Postmarketing Activities

No post marketing activities have been proposed for this application.