Summary Basis for Regulatory Action

Date:	February 28, 2024
From:	Virginie Dujols, Ph.D., Chair of the Review Committee
BLA/ STN#:	125803/0
Applicant Name:	Roche Diagnostics 9115 Hague Road Indianapolis, IN 46256
Date of Submission:	May 01, 2023
MDUFA Goal Date:	February 29, 2024
Proprietary Name:	Elecsys Anti-HCV II

Established Name (common or usual name): Elecsys HCV 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-HCV II is an in vitro immunoassay for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum and plasma. Elecsys Anti-HCV 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**mmunoassa**y** "ECLIA" is intended for use with **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.

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

Review Office Signatory Authority: Anne Eder, MD, PhD; Director, 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.

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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* • *Non-Clinical*	 Iwona Fijalkowska Viswanath Ragupathy Nitin Verma Xue Wang	 January 25, 2024 December 18, 2023 January 03, 2024 September 29, 2023
Statistical Review • *Clinical and Non-Clinical (OBPV/DB/DNCE)*	Linye Song	October 25, 2023
CMC Review • *CMC (OBRR/DETTD)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DBSQC)* • Establishment Inspection Report(s) (*OCBQ/DMPQ*)	 Kavita Singh Prajakta Varadkar Claire Wernly Prajakta Varadkar	 January 19, 2024 February 7, 2024 November 27, 2023 February 7, 2024
Labeling Review(s) • *APLB (OCBQ/APLB)* • (*OBRR/DETTD*)	 Sadhna Khatri Virginie Dujols	 December 14, 2023 January 10, 20243
Lot Release Protocols/Testing Plans/Testing Panel (*OCBQ/DBSQC*)	George Kastanis Moussa Kourout	February 2, 2024 February 27, 2024
Bioresearch Monitoring Review (*OCBQ/DIS*)	Yakubu Wangabi Kanaeko Ravenell	January 12, 2024 January 12, 2024
Software and Instrumentation (*OBRR/DETTD*)	Hongqiang Hu	December 28, 2023
Other living donor claim (OTP/DHT)	Hanh Khuu	January 02, 2024

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1. Introduction

The Elecsys Anti-HCV II assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4), Germany. This biologics license application (BLA) for the Elecsys Anti-HCV II assay from Roche Diagnostics, 9115 Hague Road Indianapolis, IN 46250, USA was received on May 01, 2023.

The application was assigned the number STN 125803/0 and granted a standard 10-month review status with a goal date of February 29, 2024. The application was filed June 05, 2023, and the mid-cycle meeting took place on September 28, 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	Regulatory Events / Milestones	Amendment to BL125803
May 01, 2023	BLA application receipt	/0
May 01, 2023	Acknowledgement letter	
May 05, 2023	RD provided updates to the serology controller software from version 1.0.3 to version 1.1.0	/1
May 10, 2023	FDA IR – analytical: request of raw analytical data	
May 12, 2023	*RD response to IR dated May 10, 2023*	/2
May 17, 2023	FDA IR – administrative: request for missing information on clinical sites in FDA Form 356	
May 18, 2023	*RD response to IR dated May 17, 2023*	/3
June 04, 2023	Filing notification letter	
July 20, 2023	FDA IR – analytical: request for clarifications of stability of analytical samples, reagents, controls and calibrators	
July 31, 2023	*RD response to IR dated July 20, 2023*	/5
August 10, 2023	FDA IR – microbiology: request for bioburden and AET testing follow-up	

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Date	Regulatory Events / Milestones	Amendment to BL125803
August 18, 2023	*RD partial response to IR (the rest of the bioburden testing data is in Amendment 12)*	/6
August 30, 2023	FDA IR – analytical: request for clarification regarding several analytical samples	
September 11, 2023	*Roche response to IR dated August 30, 2023*	/7
September 19, 2023	FDA IR – testing: request for a lot release protocol template	
September 20, 2023	*RD response to IR dated September 19, 2023*	/8
September 25, 2023	FDA IR – testing: request for confirmation of shipping address for blinded panels	
September 26, 2023	*RD response to IR dated September 25, 2023*	/9
October 12, 2023	FDA IR – analytical: request for clarification of matrix equivalence study	
October 16, 2023	*RD response to IR dated October 12, 2023*	/10
October 17, 2023	FDA IR – analytical: request for additional clarification of matrix equivalence study	
October 20, 2023	*RD response to IR dated October 17, 2023*	/11
October 30, 2023	*RD provided additional bioburden testing to IR dated August 10, 2023*	/12
November 08, 2023	FDA IR – clinical: request for clinical failure rates	
November 13, 2023	*RD response to IR dated November 08, 2023*	/13
November 16, 2023	FDA IR – analytical: request for clarification of transport stability temperature	
November 21, 2023	*RD response to IR dated November 16, 2023*	/14
December 06, 2023	FDA IR – analytical: request for clarification of LoB/LoD plasma studies	
December 08, 2023	*RD response to IR dated December 06, 2023*	/15
January 08, 2024	FDA IR – CMC: request for the correct environmental impact document	
January 08, 2024	*RD response to IR dated January 08, 2024*	/16
January 19, 2024	FDA IR – testing: request for an updated Lot Release Template	
January 29, 2024	*RD response to IR dated January 19, 2024*	/17
January 29, 2024	*RD provided lot release contact info*	/19
February 13, 2024	*RD provided partial blinded panel results*	/20
February 26, 2024	*RD provided complete blinded panel results*	/21
February 26, 2024	*RD provided all final labeling: PI, outer carton labels, vial labels and value sheets*	/22

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2. Background

The Elecsys Anti-HCV II assay is a qualitative serologic sandwich immunoassay intended for the detection of anti-HCV antibodies in human serum, plasma and source plasma. The antibodies are detected using peptides and recombinant proteins representing HCV core, NS3 and NS4 antigens, and the detection is based on the electrochemiluminescence immunoassay (ECLIA) principle. Additional controls, calibrators and general use reagents are also required to perform the assay and described in the CMC section below.

This assay is designed to be performed on the **cobas e** 801 instrument, a high throughput, fully automated immunoassay analyzer that provides routine and priority processing while allowing continuous access and automated retesting. The **cobas e** 801 Immunoassay Analyzer Instrument incorporates a dedicated software package for instrument control, data collection, results analysis, calibration, quality control, and service software. Results are determined automatically by the Elecsys software based on the comparison of the electrochemiluminescence signal of the sample to the signal obtained by an anti-HCV 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 (signal sample/cutoff). Samples with a S/CO <1.00 are considered non-reactive for anti-HCV specific antibodies and do not need further testing. Samples with a S/CO ≥1.00 are considered initially reactive on the Elecsys Anti-HCV II. All initially reactive samples are automatically retested in duplicate using the Elecsys Anti-HCV 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-HCV II assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Elecsys Anti-HCV II assay is manufactured at the Roche Diagnostics GmbH facilities in Germany located at (b) (4)
Sandhofer Strasse 116, Mannheim, 68305. The third site is a distribution facility located at Roche Diagnostics Operations, (b) (4)

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The Elecsys Anti-HCV II test kit (List Number 03290352) consists of 16 reagent cassettes (**cobas e** pack), each containing components M, R1, and R2, and two identical calibrator packs, each containing the components AHCVB Cal1 and AHCVB 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-) recombinant HCV specific antigens
- AHCV2B Cal1: Non-reactive calibrator 1, human serum negative for anti-HCV antibodies
- AHCV2B Cal2: Reactive calibrator 2, human serum positive for anti-HCV antibodies

PreciControl Anti-HCV (List number 03290379), supplied separately, is used for quality control of Elecsys Anti-HCV II. The control kit consists of the following components:

- PC AHCV1 B: Negative control, human serum non-reactive for anti-HCV antibodies
- PC AHCV2 B: Positive control, human serum reactive for anti-HCV antibodies

PreciControl Anti-HCV Release (PC AHCVR; List number 09366652190), identical to PC AHCV2 B, supplied separately, is used as a release control and consists of human serum reactive for anti-HCV antibodies.

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 (List number 11298500160): System cleaning solution.
- Liquid Flow Cleaning Cup (List number 07485425001): Cups to supply ISE Cleaning Solution/Elecsys SysClean.
- PreClean II M (List Number 06908853190): Wash solution.
- PreWash Liquid Flow Cleaning Cup (List number 07485433001): Cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit.
- ProCell II M (List number 06908799190): System reagent for generating electrochemical signal.

- Reservoir cup (List number 07485409001): Cups to supply ProCell II M and CleanCell M solutions.

b) Testing Specifications
The analytical methods and their validations and/or qualifications were reviewed for the Elecsys Anti-HCV II assay and found to be adequate for their intended use.

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

d) Facilities Review/Inspection
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 the Elecsys Anti-HCV II assay are summarized and presented in Table 3.

Table 3. Manufacturing facilities for Elecsys Anti-HCV II

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification /Results
Roche Diagnostics (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 Strasse 116, 68305 Mannheim, Germany *Labeling and final assembly of the Elecsys Anti-HCV II kit and PreciControls. 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

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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 (CDRH) conducted a pre-license inspection at Roche Diagnostics GmbH, (b) (4) , Germany in (b) (4) . The inspection covered the Warehouse and the Quality Control Laboratories associated with the subject BLA. All FDA Form-483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

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

Roche Diagnostics GmbH, Mannheim, Germany

ORA/Office of Pharmaceutical Quality Operations (OPQO) 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. 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 pro** serology solution User Guide version 1.5.

b) Device Description

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

c) Risk Management

Risks related to donor test results, exposure of user to infectious disease agents, chemical, physical and environmental hazards were evaluated. Major hazards include incorrect results, i.e., false positive and false negative donor test results, and moderate hazards include delayed results and physical hazards to the user/operator. The final risk profile of the **cobas e** 801 analyzer includes 0 red (unacceptable) risks, 15 yellow risks (that required assessment of acceptability), and 242 green (acceptable) risks. Of the 15 yellow risks, four are related to false negative results (due to wrong consumables placement, incorrect instrument processing, and non-conforming lab facilities), one is related to false positive results (due to incorrect instrument processing; for competitive assays only and irrelevant to the Elecsys Anti-HCV II test results) and 10 are related to the use of a **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-HCV 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 in BQ170139/1, the applicant submitted a software update for the Serology Controller software from version 1.0.3 to 1.1.0. The update includes automation of the onboard stability and usage tracking of calibrator/control material, and improvements from usability studies. The update does not change critical assay specific parameters such as volumes of reagents used, time for incubations, or time to signal readout. Thus, clinical data acquired using software version 1.0.3 and submitted for review in the current application for Elecsys Anti-HCV II are not affected 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) .

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a) Precision Studies

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

- One anti-HCV antibody negative specimen at target level (b) (4) S/CO
- One anti-HCV antibody high-negative specimen at target level (b) (4) S/CO
- Two anti-HCV antibody low positive specimens at target level (b) (4) S/CO
- Two anti-HCV antibody positive specimens at target level (b) (4) S/CO
- PreciControl AHCV1 B at target level (b) (4) S/CO
- PreciControl AHCV2 B positive at approximate (b) (4) S/CO

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

Sample	Mean S/CO	N	Repeatability SD [S/CO]	Repeatability CV [%]	Within Laboratory Precision SD [S/CO]	Within Laboratory Precision CV [%]
HSP 1	0.0356	84	0.000432	1.2	0.000589	1.7
HSP 2	0.893	84	0.0237	2.7	0.0260	2.9
HSP 3	1.12	84	0.0178	1.6	0.0225	2.0
HSP 4	1.39	84	0.0285	2.1	0.0300	2.2
HSP 5	5.79	84	0.0810	1.4	0.101	1.7
HSP 6	7.69	84	0.155	2.0	0.155	2.0
PC AHCV1 B	0.0471	84	0.000656	1.4	0.000793	1.7
PC AHCV2 B	3.38	84	0.0292	0.9	0.0429	1.3

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

The data provided support an acceptable within-laboratory precision of Elecsys Anti-HCV II assay.

b) Limit of Detection

(b) (4)

(b) (4)

c) Seroconversion Sensitivity

The seroconversion sensitivity of the Elecsys Anti-HCV II assay was compared to the sensitivity of an FDA-licensed assay. One lot of the Elecsys Anti-HCV II assay was used to test a total of 26 seroconversion panels. For 10 of the 26 panels, the first reactive time point for the Elecsys Anti-HCV II assay coincided with the first reactive time point for the comparator assay.

There were 29 discordant panel members across 15 panels, where the Elecsys Anti-HCV II assay detected seroconversion at an earlier bleed than the comparator assay. This discordance in detection of seroconversion by Elecsys Anti-HCV II assay compared to the comparator assay may be due to Elecsys Anti-HCV II using recombinant antigens representing HCV core, NS3, and NS4, where the optimized NS3 antigen has been developed for earlier detection capability. There were two discordant panel members in one panel, where the Elecsys Anti-HCV II assay detected seroconversion at a later bleed than the comparator assay. These two discordant specimens were also evaluated on two supplemental NAT assays and determined to be non-reactive. The summary of the results obtained from 26 commercially available seroconversion panels is presented in the Table 5.

Table 5: Seroconversion Sensitivity

Panel ID	Comparator Nonreactive	Comparator Reactive	Elecsys Anti-HCV II Nonreactive	Elecsys Anti-HCV II Reactive	Difference in bleeds Elecsys Anti-HCV II vs comparator*
PHV910	1	3	1	3	0
PHV911	1	3	1	3	0
PHV912	3	0	0	3	-3
PHV913	4	0	2	2	-2
PHV914	6	3	3	6	-3
PHV915	2	2	1	3	-1
PHV917	3	6	3	6	0
PHV918	6	1	5	2	-1
PHV919	4	3	0	7	-4

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Panel ID	Comparator Nonreactive	Comparator Reactive	Elecsys Anti-HCV II Nonreactive	Elecsys Anti-HCV II Reactive	Difference in bleeds Elecsys Anti-HCV II vs comparator*
PHV920	2	7	2	7	0
PHV922	2	4	4	2	+2
PHV923	4	2	2	4	-2
PHV924	3	3	3	3	0
PHV925	4	1	2	3	-2
PHV926	4	1	0	5	-4
Zeptom6213	8	2	7	3	-1
Zeptom6214	8	5	7	6	-1
Zeptom6215	3	1	3	1	0
Zeptom6222	7	1	6	2	-1
Zeptom6224	4	2	2	4	-2
Zeptom9041	4	4	4	4	0
Zeptom9044	4	2	3	3	-1
Zeptom9045	6	2	5	3	-1
Zeptom9046	1	4	1	4	0
Zeptom9047	6	4	6	4	0
Zeptom9054	9	1	9	1	0

*≤ -1 = Elecsys Anti-HCV II one bleed earlier, 0 = equal, ≥ +1 = Elecsys Anti-HCV II one bleed later

d) Genotype Detection

Testing was performed to evaluate the ability of the Elecsys Anti-HCV II assay to detect antibodies to known HCV genotypes. A total of (b) (4) pre-selected anti-HCV positive specimens of known genotype (genotypes 1-6) obtained from commercial vendors were tested once using the Elecsys Anti HCV II assay. All (b) (4) specimens were repeatedly reactive using the Elecsys Anti HCV II assay (b) (4) S/CO). The Elecsys Anti-HCV II assay detects common HCV genotypes.

e) Endogenous Interferences (Spiked)

Assay performance was evaluated in samples with high levels of spiked interferents (hemoglobin, intralipid (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 of the Elecsys Anti-HCV II with donor specimens containing up to (b) (4) of hemoglobin, (b) (4) of intralipid (lipemia), (b) (4) of bilirubin, and (b) (4) of total protein. In addition, a negative control, and high, medium, and low positive samples were spiked with biotin, where the highest concentration tested for interference was (b) (4). No interference was observed up to the maximum biotin concentration tested of (b) (4) using the Elecsys Anti-HCV II assay.

f) Endogenous Interferences (Native)

Assay performance was evaluated in specimens containing naturally occurring elevated levels of hemoglobin (hemolyzed), triglycerides (lipemia), bilirubin, total protein (albumin), and rheumatoid factor. A total of (b) (4) anti-HCV negative serum specimens were tested for each interferent. 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 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)

g) Cross Reaction/Analytical Specificity

Analytical specificity of the Elecsys anti-HCV II assay was evaluated by testing specimens with conditions or disease states unrelated to a hepatitis infection. A total of 280 samples containing potentially interfering factors were spiked individually with anti-HCV 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 HAV, HEV, HIV, HBV, HVD, HTLV-I/II, CMV, HSV IgG/IgM, Rubella IgG/IgM, and EBV
- Positive for antibodies against Candida, Chlamydia, *E. coli*, Toxoplasma gondii, Treponema Pallidum (Syphilis), Parvovirus, and Lupus
- Containing antinuclear antibodies (ANA) and elevated titers of rheumatoid factor
- Containing heterophilic and human anti-mouse antibodies (HAMA)
- After vaccination against influenza, (b) (4), HBV
- For (b) (4) non-viral liver disease
- From pregnant woman, multiparous pregnancies

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

h) Drug interference

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

i) Prozone (Hook Effect)

Assay performance was evaluated using (b) (4) . The data demonstrate acceptable performance of the assay as all high titer specimens tested reactive. No false negative results were observed due to hook effect.

j) Serum and Plasma Comparison

The impact of anticoagulants on the performance of the Elecsys anti-HCV II assay was evaluated using (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) for CPD) individual non-reactive donor specimens and (b) (4) A total of (b) (4) for CPD) negative samples were tested from unique native samples.

The assay performance when evaluated using 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-, K_2-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.

k) Specimen Storage

Assay performance 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 using serum and plasma specimens. The target analyte concentrations ranged from (b) (4) S/CO for negative samples and from (b) (4) S/CO to (b) (4) S/CO for anti-HCV positive samples. The data demonstrate acceptable performance of the assay supporting the use of serum and plasma specimens that were stored at 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 12 months, and up to (b) (4) freeze/thaw cycles. These data support the storage claims in the package insert.

l) Specimen Processing

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

m) 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-HCV negative (n= (b) (4) and anti-HCV low and high positive (n= (b) (4) – and compared to specimens stored at unstressed conditions. The target concentrations ranged from (b) (4) S/CO for positive samples. 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.

n) Kit Lot Calibration and On-Board Calibration Stability

Calibration of the Elecsys Anti-HCV II assay must be performed once per reagent lot using AHCVB Cal1, AHCVB Cal2 and fresh reagents. Lot calibration stability was validated using an Elecsys Anti-HCV 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-HCV negative (n= (b) (4), anti-HCV spiked (n= (b) (4) at analyte levels ranging from (b) (4) S/CO) for positive samples, 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, a (b) (4) serum specimens panel – anti-HCV negative (n= (b) (4), anti-HCV positive (n= (b) (4) at analyte levels ranging from (b) (4) S/CO), and (b) (4) PreciControls – was utilized by measuring in (b) (4) to test the stability of Elecsys Anti-HCV II kit components stored on-board of 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.

o) Reagent Stability Studies

Reagent real time stability was determined using (b) (4) Elecsys Anti-HCV 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-HCV negative (n=(b) (4), anti-HCV positive (n=(b) (4) at analyte levels ranging from (b) (4) S/CO), and (b) (4) PreciControls – were tested in (b) (4) and compared to unstressed reagents. The data provided and reviewed demonstrate acceptable performance of the assay supporting a reagent stability claim of up to (b) (4) months at 2 to 8°C.

In addition, a sample panel of (b) (4) serum specimens – anti-HCV negative (n=(b) (4), anti-HCV positive (n=(b) (4) at analyte levels ranging from (b) (4) S/CO), and (b) (4) PreciControls – was utilized to evaluate the stability of the Elecsys Anti-HCV II kit components when stored on-board at (b) (4) for (b) (4) days. 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 31 days at (b) (4) and a transportation claim of up to one week.

p) 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-HCV negative (n=(b) (4) and one each of anti HCV antibody low and high positive – and compared with samples that were equilibrated at (b) (4). The target concentrations obtained for positive samples ranged from (b) (4) S/CO. The data demonstrate acceptable performance of the Elecsys Anti-HCV II assay supporting the use of specimens and kit components without first equilibrating for (b) (4)

q) Calibrator Stability

Calibrators AHCVB Cal1 and AHCVB Cal2 are supplied ready-for-use in vials compatible with the system. Stability of the calibrators was evaluated by measuring them in (b) (4) after storage under various conditions. The data demonstrate acceptable performance of the calibrators supporting stability claims of storage up to (b) (4) hours on-board of the analyzer at 20°C to 25°C, and up to 8 weeks at 2°C to 8°C after first opening.

r) PreciControl Stability

PreciControls PC AHCV1 B and PC AHCV2 B are supplied ready-for-use in vials used for monitoring the accuracy of the Elecsys Anti-HCV II assay. Stability of the

PreciControls was evaluated by measuring them after storage at various conditions and compared to t = 0. The data provided and reviewed demonstrate acceptable performance of the PreciControls supporting stability claims of storage up to 12 months at 2°C to 8°C, up to 5 hours on-board of the analyzer at 20°C to 25°C, and up to (b) (4) at 2°C 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.

s) 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. The 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 four 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.

t) Cadaveric Studies

No cadaveric claims were sought by Roche in this BLA.

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

u) Microbial Challenge

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

6. Clinical Studies

Clinical studies were conducted to evaluate assay specificity, sensitivity and reproducibility to demonstrate performance in the intended use population of the Elecsys Anti-HCV II assay. Testing was performed at three blood donor testing laboratories. Four lots of the Elecsys Anti-HCV II Reagent kit were used. Three lots of the PreciControl Anti-HCV and three lots of the PreciControl Anti-HCV Release were utilized for the studies at each of the testing sites.

a) Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Elecsys Anti-HCV II assay on the **cobas e** 801 analyzer using an FDA-licensed comparator assay by testing a total of 14,286 specimens. All donors enrolled were evaluated and no donation was excluded.

Of the 14,286 specimens tested, 5,571 were fresh serum and 5,713 were fresh plasma specimens, all from voluntary blood donors collected at 21 blood centers from 9,468 repeat donors and from 1,816 first time donors. An additional 3,002 plasmapheresis

specimens were collected at six blood centers. The testing was performed at three clinical sites using the Elecsys Anti-HCV II assay and an FDA-licensed comparator assay.

There were 25 initially reactive specimens using the Elecsys Anti-HCV II assay, and all initially reactive samples were repeat reactive – 11 serum specimens, 8 plasma specimens and 6 plasmapheresis specimens. Repeatedly reactive specimens were further tested using supplemental assays. Out of the 25 Elecsys repeat reactive specimens, 18 had a final specimen status of negative (18 false positive results in Elecsys Anti-HCV II) and 7 had a final specimen status of positive.

The initial and repeat reactive rates for the Elecsys Anti-HCV II assay were 0.17% (25/14286) - the initial and repeat reactive rates for the serum specimens were 0.20 % (11/5571), the initial and repeat reactive rates for the plasma specimens were 0.14 % (8/5713), and the initial and repeat reactive rates for the plasmapheresis samples were 0.20 % (6/3002).

The specificity of the Elecsys Anti-HCV II assay relative to the final anti-HCV antibody status in blood and plasmapheresis donors was calculated to be 99.87% (14259/14277) with a 95% confidence interval (CI) of 99.80% to 99.92% as presented in Table 6.

Table 6: Elecsys Anti-HCV II Clinical Study. Specificity of Elecsys Anti-HCV II in Donors

Specimen category	Number tested	Number IR (% of Total)	Number RR (% of Total)	Number Confirmed Positive (% of RR)	Specificity (%)[a] (95% CI)
Blood Donors Serum	5571	11 (0.20)	11 (0.20)	6 (54.55)	99.91 (99.79 - 99.96) 5560/5565
Blood Donors Plasma	5713	8 (0.14)	8 (0.14)	1 (12.50)	99.88 (99.75 - 99.94) 5704/5711
Source Plasma donors	3002	6 (0.20)	6 (0.20)	0 (0.00)	99.80 (99.56 - 99.91) 2995/3001
Total Donors	14286	25 (0.17)	25 (0.17)	7 (28.00)	99.87 (99.80 - 99.92) 14259/14277

IR = initially reactive; RR = repeatedly reactive; CI = confidence interval.

[a] Based on supplemental test results for the 25 repeatedly reactive specimens (11 specimens were serum, 8 specimens were plasma, 6 specimens were source plasma)

b) Clinical Sensitivity

The Elecsys Anti-HCV II assay sensitivity was established by analyzing test results for 923 specimens that were identified as anti-HCV positive (anti-HCV positive, HCV chronic, and HCV genotypes 1-6). The testing was performed at three clinical sites using the Elecsys Anti-HCV II assay and a comparator FDA-licensed assay. Elecsys repeatedly reactive specimens were confirmed with a supplemental FDA-licensed assay.

Of the 923 tested specimens, 8 specimens were non-reactive with the comparator FDA-licensed assay and were excluded, leaving 915 specimens for the sensitivity evaluation. Of the 915 specimens, 3 specimens were negative on the Elecsys Anti-HCV II assay and positive on the comparator assay.

The overall sensitivity was determined to be 99.67% (912/915) with a 95% confidence interval of 99.04% to 99.89% as presented in Table 7.

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

Specimen category	Number tested	Number positive	Number RR (% of Total)	Number of RR Confirmed Positive (% of RR)	Sensitivity (%) (95% CI)
HCV Genotypes 1-6	101	101	101 (100)	101 (100)	100.00 (96.34 - 100.00) 101/101
HCV Positive	695	695	692 (99.57)	692 (100)	99.57 (98.74 - 99.85) 692/695
HCV Positive (Chronic)	119	119	119 (100)	119 (100)	100.00 (96.87 -100.00) 119/119
Total	915	915	912 (99.67)	912 (100)	99.67 (99.04 - 99.89) 912/915

RR = Repeatedly Reactive

c) Reactivity in Increased Risk Populations

The Elecsys Anti-HCV II assay performance in an untested increased risk population for hepatitis was evaluated using a total of 409 specimens. There were 291

specimens that were non-reactive with both the Elecsys Anti-HCV II assay and with an FDA-licensed comparator assay.

A total of 118 specimens were repeatedly reactive on the Elecsys Anti-HCV II assay with 112 specimens confirmed positive based on supplemental testing using FDA-licensed assays. Six of the repeat reactive specimens were confirmed to be false positive results using FDA-licensed assays as comparator and supplemental assays as summarized in Table 8.

Table 8. Testing in Increased Risk Cohorts and Endemic Areas for Elecsys Anti-HCV II

Specimen Category	Number Tested	Number IR (% of Total)	Number RR (% of Total)	Number Confirmed Positive (% of RR)
Individuals at Increased Risk for Hepatitis Infection	409	118 (28.85)	118 (28.85)	112 (94.92)

IR = Initially Reactive; RR = Repeatedly Reactive

d) Reproducibility Studies

Reproducibility of the Elecsys Anti-HCV II assay was evaluated at three sites with (b) (4) per site using three lots each of the Elecsys Anti-HCV II assay, and one lot each of PreciControl Anti-HCV 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 Anti-HCV 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-HCV antibody sample at target level (b) (4) S/CO
- One high anti-HCV antibody sample at target level (b) (4) S/CO

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

- PreciControl AHCV1 B negative at target level (b) (4) S/CO
- PreciControl AHCV2 B positive 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 Anti-HCV II assay. The results of the reproducibility panel and control testing demonstrate that the Elecsys Anti-HCV II assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 9.

Summary Basis for Regulatory Action

Tables 9: Overall Repeatability/Reproducibility for Elecsys Anti-HCV II

a. Repeatability, Between Run and Between Day Precision:

	Mean S/CO	N	Repeatability SD	Repeatability CV [%]	Between Run SD	Between Run CV [%]	Between Day SD	Between Day CV [%]
HSP 8	1.81	270	0.023	1.25	0.011	0.592	0.016	0.898
HSP 9	11.6	269	0.140	1.21	0.104	0.899	0.124	1.08
PC AHCV1 B	0.047	270	0.001	1.12	0.000	0.314	0.001	1.76
PC AHCV2 B	3.57	270	0.040	1.12	0.034	0.9	0.027	0.746

HSP 8 = low anti-HCV antibody human specimen, HSP 9 = high anti-HCV 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:

	Mean S/CO	N	Intermediate Precision SD	Intermediate Precision CV [%]	Between Site SD	Between Site CV [%]
HSP 8	1.81	270	0.030	1.65	0.005	0.256
HSP 9	11.6	269	0.214	1.85	0.038	0.324
PC AHCV1 B	0.047	270	0.001	2.10	0.000	0.722
PC AHCV2 B	3.57	270	0.059	1.65	0.013	0.368

c. Between Lot and Overall Reproducibility:

	Mean S/CO	N	Between Lot SD	Between Lot CV [%]	Reproducibility SD	Reproducibility CV [%]
HSP 8	1.81	270	0.108	5.97	0.113	6.20
HSP 9	11.6	269	0.516	4.46	0.560	4.84
PC AHCV1 B	0.047	270	0.001	2.68	0.002	3.48
PC AHCV2 B	3.57	270	0.091	2.54	0.109	3.05

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 14, 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-HCV II assay.

b) Risk/Benefit Assessment
The risk/benefit analysis demonstrates that the benefit of the Elecsys Anti-HCV 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 99.67% (95% CI of 99.04 – 99.89), indicating a low probability of a false negative result. Among 14286 blood and plasmapheresis donors tested with the Elecsys Anti-HCV II assay, the assay specificity of 99.87% (95% CI of 99.80 – 99.92) 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.