February 8, 2019

Roche Diagnostics Operations (RDO)
Noel Mencias
Principal, Regulatory Affairs
9115 Hague Road
Indianapolis, IN 46250

Re: K183517
Trade/Device Name: Ammonia II
Regulation Number: 21 CFR 862.1065
Regulation Name: Ammonia test system
Regulatory Class: Class I, reserved
Product Code: JIF
Dated: December 17, 2018
Received: December 18, 2018

Dear Noel Mencias:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kellie B. Kelm -S

for Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k183517

Device Name
Ammonia II

Indications for Use *(Describe)*
The Ammonia II assay is an enzymatic in vitro test for the quantitative determination of ammonia in human plasma on Roche/Hitachi cobas c systems.

Ammonia measurements are used in the diagnosis and treatment of severe liver disorders, such as cirrhosis, hepatitis, and Reye's syndrome.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Ammonia II

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the Ammonia II assay

Submitter Name	Roche Diagnostics
Address	9115 Hague Road Indianapolis, IN 46250-0457
Contact	Noel B. Mencias Phone: (317) 521-3172 FAX: (317) 521-2324 Email: noel.mencias@roche.com
Date Prepared	December 17, 2018
Proprietary Name	Ammonia II
Common Name	Ammonia
Classification Name	Ammonia test system
Product Codes, Regulation Numbers	JIF, 21 CFR 862.1065
Predicate Devices	Beckman Coulter Ammonia
Establishment Registration	For the Ammonia II assay, the establishment registration number for Roche Diagnostics GmbH in Mannheim, Germany is 9610126, and for Penzberg, Germany, 9610529. The establishment registration number for Roche Diagnostics in the United States is 1823260.

1. DEVICE DESCRIPTION

The Ammonia II (NH3L2) assay is an enzymatic in vitro test for the quantitative determination of ammonia in human plasma on Roche/Hitachi **cobas c** systems. The Ammonia II assay is an enzymatic method, with glutamate dehydrogenase.

2. INDICATIONS FOR USE

The Ammonia II assay is an enzymatic in vitro test for the quantitative determination of ammonia in human plasma on Roche/Hitachi **cobas c** systems.

Ammonia measurements are used in the diagnosis and treatment of severe liver disorders, such as cirrhosis, hepatitis, and Reye's syndrome.

3. TECHNOLOGICAL CHARACTERISTICS

The Ammonia II assay is an enzymatic method, with glutamate dehydrogenase. Glutamate dehydrogenase (GLDH) catalyzes the reductive amination of 2-oxoglutarate with NH4+ and NADPH to form glutamate and NADP+. The concentration of the NADP+ formed is directly proportional to the ammonia concentration. It is determined by measuring the decrease in absorbance.

The following tables compare the Ammonia II (NH3L2) assay with its predicate device, SYNCHRON Systems Ammonia Reagent (k003196).

Table 1: Assay Comparison

Feature	SYNCHRON Systems Ammonia Reagent (k003196)	Ammonia II
Intended Use	AMM reagent, when used in conjunction with UniCel® DxC 600/800 System(s) and SYNCHRON® Systems Ammonia Calibrators, is intended for the quantitative determination of ammonia concentration in human plasma.	The Ammonia II assay is an enzymatic in vitro test for the quantitative determination of ammonia in human plasma on Roche/Hitachi **cobas c** systems.

Feature	SYNCHRON Systems Ammonia Reagent (k003196)	Ammonia II
Test Principle	The SYNCHRON® System(s) automatically proportions the appropriate sample and reagent volumes into a cuvette. The ratio used is one part sample to 6 parts reagents. The system monitors the change in absorbance at 340 nanometers. This change in absorbance is directly proportional to the concentration of ammonia in the sample and is used by the SYNCHRON® System(s) to calculate and express the ammonia concentration.	Enzymatic method, with glutamate dehydrogenase. Glutamate dehydrogenase (GLDH) catalyzes the reductive amination of 2-oxoglutarate with NH4+ and NADPH to form glutamate and NADP+. The concentration of the NADP+ formed is directly proportional to the ammonia concentration. It is determined by measuring the decrease in absorbance.
Instrument	UniCel DxC 600/800 System(s) and SYNCHRON Systems	cobas c 501
Reagent Composition	REAGENT CONSTITUENTS α-Ketoglutarate 3.23 mmol/L ADP 1.9 mmol/L NADPH 0.22 mmol/L GLDH (Beef liver) >10 U/L	R1 BICINEa) buffer: 300 mmol/L, pH 8.3; GLDH (microbial): ≥ 16.7 µkat/L; detergents; preservative R3 GLDH (microbial): ≥ 5.0 µkat/L; 2-oxoglutarate: 78 mmol/L; NADPH: ≥ 1.3 mmol/L; nonreactive buffer a) BICINE = N,N-bis(2-hydroxyethyl)-glycine
Sample Type/Matrix	Sodium Heparin EDTA	K2- and K3-EDTA plasma
Calibrator	SYNCHRON Systems Ammonia Calibrators	Ammonia/Ethanol/CO2 Calibrator
Calibration Interval	Under typical operating conditions the AMM reagent cartridge must be calibrated every 5 days and also with certain parts replacement or maintenance procedures, as defined in the UniCel DxC 600/800 System Instructions For Use (IFU) manual.	Calibration frequency 2-point calibration - after lot change - automatically every 14 days - as required following quality control procedures

Feature	SYNCHRON Systems Ammonia Reagent (k003196)	Ammonia II
Controls	At least two levels of control material	Ammonia/Ethanol/CO2 Control Normal Ammonia/Ethanol/CO2 Control Abnormal
Traceability/Standardization	Ammonia measurand (analyte) in this calibrator is traceable to the manufacturer's selected measuring method. The traceability process is based on prEN ISO 17511.	This method has been standardized against a primary standard.
Reagent Stability	AMM reagent, when stored unopened at +2°C to +8°C, will remain stable until the expiration date printed on the label.	Shelf life at 2-8 °C: See expiration date on cobas c pack label.
Reagent On-Board Stability	Once opened, the reagent is stable for 30 days at +2°C to +8°C unless the expiration date is exceeded.	On-board in use and refrigerated on the analyzer: 16 weeks
Measuring Range	16 – 1700 µg/dL (9 – 1000 µmol/L)	10-1000 µmol/L (17-1703 µg/dL)
Lower Limits of Measurement	lower limit of 9 µmol/L (16 µg/dL)	Limit of Blank = 10 µmol/L (17 µg/dL) Limit of Detection = 10 µmol/L (17 µg/dL) Limit of Quantitation = 10 µmol/L (17 µg/dL)
Sample Stability	Tubes should be filled completely, mixed gently by inversion, placed on ice, centrifuged immediately for 10 minutes at an RCF of 1500G and analyzed within 30 minutes. Samples should not be frozen. The tubes should be tightly stoppered at all times.	Stability in plasma: 30 min at 15-25 °C 2 hours at 2-8 °C 3 days at −20 ± 5 °C 4 weeks at (−60)-(−90) °C (at least)

4. NON-CLINICAL PERFORMANCE EVALUATION

The following performance data were provided in support of the substantial equivalence determination:

Precision according to CLSI EP05-A3

Detection Limit: LoB, LoD, LoQ according to CLSI EP17-A2

Linearity according to CLSI EP06-A

Endogenous Interferences

Exogenous Interferences – Drugs

Method Comparison to Predicate

Matrix Comparison - Anticoagulants.

4.1. Precision

4.1.1. Repeatability and Intermediate Precision

Precision experiments were performed in accordance with CLSI Guideline EP5-A3. Two aliquots per run, two runs per day for ≥ 21 days were performed on the same analyzer using 3 lots of reagent. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated. The samples were randomized in each run separately. For each sample, the following were calculated: Mean, Repeatability and intermediate precision as CV and SD values, and the upper 95% confidence interval for SD and CV values.

Table 2: Repeatability Summary

Specimen	Mean (µmol/L)	SD (µmol/L)	CV (%)
AMM-N	66.6	1.40	2.1
AMM-P	243	3.45	1.4
Human Plasma 1	26.0	1.26	4.8
Human Plasma 2	57.7	1.63	2.8
Human Plasma 3	110	1.62	1.5
Human Plasma 4	492	4.12	0.8
Human Plasma 5	863	9.54	1.1

Table 3: Intermediate Precision Summary

Specimen	Mean (µmol/L)	SD (µmol/L)	CV (%)
AMM-N	67.9	1.61	2.4
AMM-P	243	4.26	1.8
Human Plasma 1	26.0	1.29	4.9
Human Plasma 2	57.7	1.72	3.0

Specimen	Mean (µmol/L)	SD (µmol/L)	CV (%)
Human Plasma 3	110	1.92	1.7
Human Plasma 4	480	6.30	1.3
Human Plasma 5	853	12.4	1.5

All data passed the predetermined acceptance criteria.

4.2. Analytical Sensitivity

LoB, LoD, and LoQ were determined according to CLSI EP17-A2.

4.2.1. Limit of Blank (LoB)

Limit of Blank determines the highest observed measurement values for samples free of analyte.

For determination of LoB one analyte free sample was measured with three lots in 10-fold determination in 6 runs, distributed over 3 days, on one **cobas c** 501 analyzer. In total, 60 measurements were obtained per lot. Data analysis is based on determination of the 95th percentile of the 60 measured values

4.2.2. Limit of Detection (LoD)

The LoD determines the lower limit for samples with analyte. The LoD was determined as the lowest amount of analyte in a sample that can be detected with a 95% probability.

For determination of LoD five samples with low-analyte concentration (approximately up to 4 times the LoB) were measured with three lots in two-fold determination in 6 runs, distributed over 3 days, on one **cobas c** 501 analyzer. In total 60 measurements were obtained per lot.

4.2.3. Limit of Quantitation (LoQ)

The limit of quantitation (LoQ), according to EP17-A2 is the lowest analyte concentration that can be quantitatively determined with a stated acceptable precision and trueness under stated experimental conditions.

A low level sample Set was prepared by diluting 7 human plasma samples with water. The low level sample set was tested in 5 replicates per sample on 5 days, one run per day on one **cobas c** 501 analyzer.

Table 4: LoB, LoD, and LoQ Experimental Determination

	Result (µmol/L)	**Claim (µmol/L)**
Limit of Blank (LoB)	1.80	≤ 10 µmol/L
Limit of Detection (LoD)	3.46	≤ 10 µmol/L
Limit of Quantitation (LoQ)	9.36	≤ 10 µmol/L

All data passed the predetermined acceptance criteria.

4.3. Linearity/Assay Reportable Range

4.3.1. Regression Analysis

The linearity study was conducted to demonstrate that measurements across the claimed measuring range for each parameter are linear. The study was performed according to CLSI guideline EP06-A.

A linearity check was performed with first order (linear) regression and then with higher order models (quadratic and cubic).

Table 5: Linearity Results

Reagent Lot	**Linear Regression**
1	y = 1.003x – 2.19 correlation coefficient (r^2) = 0.9999
2	y = 1.002x – 1.30 correlation coefficient (r^2) = 1
3	y = 1.002x -1.56 correlation coefficient (r^2) = 0.9999

All data passed the predetermined acceptance criteria.

4.4. Endogenous Interferences

4.4.1. Hemolysis/Bilirubin/Lipemia/Albumin/IgG

The effects of interference by hemoglobin, lipemia (Intralipid), Albumin, Immunoglobulin (IgG) and Bilirubin on the NH3L2 test system were determined on the **cobas c** 501 analyzer using pooled human plasma samples spiked with varying levels of interferent. The resulting sample series (10 dilution steps per sample) were tested in triplicate and the median values used to calculate % recovery, by comparing the measured concentration to the expected concentration (which is the NH3L2 concentration when no interferent was added).

Table 6: Endogenous Interference Results

Substance tested	Tested Substance Approximate Concentration	Ammonia concentrations in umol/L
Hemolysis	Level 1: 114 mg/dL Level 2: 146 mg/dL	Level 1: 36.1 Level 2: 91.8
Unconjugated Bilirubin	Level 1: 69 mg/dL Level 2: 68 mg/dL	Level 1: 46.4 Level 2: 113
Conjugated Bilirubin	Level 1: 64 mg/dL Level 2: 64 mg/dL	Level 1: 40.2 Level 2: 89.1
Lipemia (Intralipid)	Level 1: 764 mg/dL Level 2: 771 mg/dL	Level 1: 51.5 Level 2: 92.7
Albumin	Level 1: 77.5 g/L Level 2: 77.2 g/L	Level 1: 47.2 Level 2: 108
Immunoglobulin (IgG)	Level 1: 71.7 g/L Level 2: 71.4 g/L	Level 1: 41.5 Level 2: 83.9

Listed are the highest levels of interferent which passed specification at the analyte concentration levels. All data passed the predetermined acceptance criteria.

4.5. Exogenous Interferences – Drugs

The purpose of this study was to evaluate drugs for potential interference with NH3L2 assay measured on the **cobas c** 501 analyzer. Two sample pools, containing a low and high concentration of NH3L2 were used. These sample pools were divided into an appropriate number of aliquots. One aliquot was not spiked with the drugs and it was used as the reference

sample for NH3L2 concentration. The NH3L2 concentration in the sample was determined with n = 3 measurements on a **cobas c** 501 analyzer.

The other sample aliquots, with either the high or low NH3L2 concentrations, are spiked with the respective amount of drug. The NH3L2 concentration of the spiked aliquots are determined in triplicate and the mean of the triplicate determinations is compared to the NH3L2 concentration determined for the reference aliquot (mean of n=3).

No interference was found at therapeutic concentrations using common drug panels with the exceptions of Cefoxitin, Sulfasalazin, and Temozolomid which were found to interfere.

4.6. Sample Matrix Comparison

The effect of the presence of anticoagulants on analyte recovery was determined by method comparison, obtained from samples drawn into different types of plasma collection tubes (K2 EDTA and K3 EDTA). For K2 EDTA and K3 EDTA 52 tubes for Lot 1 and 53 tubes for Lot 2 and 53 tubes for Lot 3 were collected and filled completely.

Method comparison K2 EDTA versus K3 EDTA were calculated. Slope, Intercept and Correlation were calculated.

Table 7: Matrix Comparison Results

Reagent Lot	Regression	Correlation (Pearson(r))
1	y = 1.002x -1.18	1.000
2	y = 0.987x – 0.77	1.000
3	y = 1.005x – 1.39	1.000

4.7. Method Comparison to Predicate

A total of 112 human plasma samples were tested in singlicate with the AMM test kit of Beckmann Coulter on Beckmann Synchron DxC 800 and the NH3L2 reagent on **cobas c** 501. The results were calculated using Passing/Bablok, and Linear regression.

Regression analysis results:

y = 1.001x – 1.90 µmol/L, r = 1.000

5. CLINICAL PERFORMANCE EVALUATION

Not applicable.

6. ADDITIONAL INFORMATION

6.1. Other Devices Marketed with This Assay

The Ammonia II assay continues to use:

Ammonia/Ethanol/CO2 Calibrator (k031880)

Ammonia/Ethanol/CO2 Control Normal (k031880)

Ammonia/Ethanol/CO2 Control Abnormal (k031880)

7. CONCLUSIONS

The submitted information in this premarket notification supports a substantial equivalence decision.