510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k123677

B. Purpose for Submission:

New device

C. Measurand:

Ammonia

D. Type of Test:

Quantitative, Enzymatic

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Vista® Ammonia Flex® reagent cartridge (AMM)
Dimension Vista® Chem 3 Calibrator (CHEM 3 CAL)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JIF	I, reserved	21 CFR 862.1065, Ammonia Test System	Chemistry (75)
JIX	II	21 CFR 862.1150, Calibrator	Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for Use below.

2. Indication(s) for use:

   The AMM method is an *in vitro* diagnostic test for the quantitative measurement of ammonia in human plasma on the Dimension Vista® System. Ammonia measurements are used in the diagnosis and treatment of severe liver disorders such as cirrhosis, hepatitis and Reye's syndrome.

   The CHEM 3 CAL is an *in vitro* diagnostic product for the calibration of Ammonia (AMM), Carbon Dioxide (CO_2) and Ethyl Alcohol (ETOH) methods on the Dimension Vista® System.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   For Use on Siemens Dimension Vista® systems only.

I. Device Description:

The Dimension Vista® Ammonia (AMM) Flex® reagent cartridge is an *in vitro* diagnostic device that consists of prepackaged reagents in a plastic cartridge for use on the Dimension Vista® System. Flex® reagent cartridges hold reagents for a test method. Each Dimension Vista® Flex has twelve wells. Each well contains α-ketoglutarate (10 mmol/L), GLDH (≥ 24 KU/L), NADPH (0.2 mmol/L) as well as buffers, stabilizers and preservatives. Reagent preparations are performed automatically on the instrument. A barcode label on the cartridge identifies the test method, lot number, expiration date and maximum number of tests for which the cartridge can supply reagent.

The Dimension Vista® Chemistry 3 Calibrator (CHEM 3 CAL) is a two level, liquid calibrator. It is packaged as a kit of six vials with three vials each of Level A and B, containing 2.5 mL per vial. The product is a multi-analyte, aqueous product containing ammonium bicarbonate, sodium carbonate and ethyl alcohol. CAL A is made by adding preservatives to purified water and CAL B is made by adding the calculated quantity of ammonium bicarbonate to purified water with preservatives, along with alcohol and sodium carbonate. This product is sold separately from the Flex® reagent cartridge.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension® Ammonia (AMON)
   Dimension Vista® Chemistry 3 Calibrator (CHEM 3 CAL)

2. Predicate 510(k) number(s):

   k863840 (AMON)
   k062334 (CHEM 3 CAL)

3. Comparison with predicate:

   Dimension Vista® AMM assay:

Similarities		
Item	Device Dimension Vista Ammonia Flex® reagent cartridge (AMM)	Predicate Dimension® Ammonia Flex® reagent cartridge (AMON) k863840
Intended Use	An in vitro diagnostic test for the quantitative measurement of ammonia in human plasma.	Same
Format	Prepackaged for use on an automated system	Same
Measurement Principle	Bichromatic rate	Same

Differences		
Item	Device Dimension Vista Ammonia Flex® reagent cartridge (AMM)	Predicate Dimension® Ammonia Flex® reagent cartridge (AMON) k863840
Measuring Range	17–1277 µg/dL	0-1700 µg/dL
Sample Type	Plasma (Lithium Heparin and EDTA)	Plasma (EDTA, Lithium Heparin, Sodium Fluoride)
Reagent Form	Liquid	Tablet
Units	µg/dL and µmol/L	µmol/L
Sample Size	20 µL	53 µL

Dimension Vista® CHEM 3 CAL:

Similarities		
Item	Device Dimension Vista® Chem 3 Calibrator (CHEM 3 CAL) (KC130A)	Predicate Dimension Vista® Chem 3 Calibrator (CHEM 3 CAL) (KC130) k062334
Intended Use	The CHEM 3 CAL is an *in vitro* diagnostic product for the calibration of Ammonia (AMM), Carbon Dioxide (CO_2) and Ethyl Alcohol (ETOH) methods on the Dimension Vista® System.	Same
Preparation	Liquid: Ready to use	Same
Storage	2 – 8 °C	Same
Traceability	AMM - ASC Grade Ammonium Sulfate ECO_2 - NIST SRM 351 ETOH - USP Grade Ethyl Alcohol	Same
Matrix	Aqueous product containing ethyl alcohol, ammonium bicarbonate and sodium carbonate	Same
Target Concentrations	CO_2: CAL A - 0 mmol/L CAL B – 50 mmol/L ETOH: CAL A – 0 mg/dL CAL B – 315 mg/dL	Same

Differences		
Item	Device Dimension Vista® Chem 3 Calibrator (CHEM 3 CAL) (KC130A)	Predicate Dimension Vista® Chem 3 Calibrator (CHEM 3 CAL) (KC130) k062334
Target Concentrations	Calibrator A: 0 µg/dL Calibrator B: 1405 µg/dL	Calibrator A: 0 µg/dL Calibrator B: 1700 µg/dL

K. Standard/Guidance Document Referenced (if applicable):

- Clinical and Laboratory Standards Institute (CLSI) Guideline EP5-A2: *Evaluation of Precision Performance of Quantitative Measurement in Methods*

- CLSI Guideline EP6-A: *Evaluation of the Linearity of Quantitative Measurement Procedures; A Statistical Approach*

- CLSI Guideline EP7-A2: *Interference Testing in Clinical Chemistry*

- CLSI Guideline EP9-A2: *Method Comparison and Bias Estimation Using Patient Samples*

- CLSI Guideline EP17-A: *Protocols for Determination of Limits of Detection and Quantitation*

- CLSI Guideline C28-A3: *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory*

- CLSI Guideline EP6-A: *Evaluation of Stability of In-Vitro Diagnostic Reagents*

L. Test Principle:

The Dimension Vista® Ammonia assay (AMM) is an enzymatic method that uses glutamate dehydrogenase (GLDH) and a stabilized NADPH analog. Ammonia reacts with α-ketoglutarate and reduced cofactor to form L-glutamate and the cofactor. The reaction is catalyzed by glutamate dehydrogenase. The decrease in absorbance due to the oxidation of the reduced cofactor is monitored at 340/700 nm and is proportional to the ammonia concentration.

$$\alpha\text{-ketoglutarate} + NH_4^+ + \text{reduced cofactor} \xrightarrow{\text{GLDH}} \text{L-glutamate} + \text{cofactor} + H_2O$$

M. Performance Characteristics (if/when applicable):

The following performance data were collected on a Dimension Vista 1500 System.

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*

   Precision testing was performed in accordance with CLSI EP5-A2. Samples consisted of three levels of Bio-Rad® Liquichek™ Ethanol/Ammonia Control and represented clinically relevant ranges of normal and elevated ammonia levels in plasma. Testing was performed over 20 days, two separate runs with two test samples for each test material. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2. The data are summarized in the following table:

Material	Mean (µg/dL)	Repeatability		Within Lab	
		Standard Deviation	% CV	Standard Deviation	% CV
Level 1	44	2.7	6.1	3.3	7.5
Level 2	186	2.3	1.2	3.2	1.7
Level 3	563	3.5	0.6	5.0	0.9

b. *Linearity/assay reportable range:*

The linear range was determined according to CLSI EP-6A. Linearity testing was performed using commercial Dimension Vista® CHEM 3 CAL Level B (high level) and was diluted by sequential mixing with CHEM 3 CAL Level A (0 calibrator). Seventeen (17) levels were prepared and tested. The observed values in each case represent the mean of 5 replicates. The range of plasma samples tested was 0 - 1392 µg/dL. Linear regression results are summarized below.

Slope	Intercept	Correlation Coefficient (r)
0.99	3.74	1.00

Based on the results of this testing and the Limit of Quantitation testing, the sponsor claims that the measurement range of the ammonia assay is 17 -1277 µg/dL.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

Ammonia in the CHEM 3 CAL calibrator is traceable to ACS grade ammonium sulfate by gravimetric method. CO_2 is traceable to NIST SRM 351. Ethyl alcohol is traceable to US Pharmacopeia Grade ethyl alcohol.

Stability:

CHEM 3 Calibrator:

Calibrator shelf life is determined in real-time. Protocols and acceptance criteria were reviewed and determined to be acceptable. The testing supports the sponsor's claimed shelf life stability of 12 months when stored at 2-8ºC.

Calibrator open and punctured vial stability are determined in real-time. Protocols and acceptance criteria were reviewed and determined to be acceptable. The testing supports the sponsor's claimed opened vial stability of 30 days when stored at 2-8ºC, and punctured vial stability of 24 hours when stored on board the Dimension Vista instrument.

Storage Recommendations are provided in the package insert.

Value Assignment:

CHEM 3 CAL calibrator is a two level calibrator product. Calibrator Level A is a nominal zero calibrator. Calibrator Level B is value assigned using standard for each analyte.

Ammonia – the assigned values for ammonia ethanol are based on results from multiple instruments and reagent lots. The ammonia assigned values for CHEM 3 CAL are the mean of a minimum of 45 replicates per level. Target ranges for ammonia are 0 ± 15 µg/dL (LoD) for Level A and 1405 ± 43 µg/dL for Level B.

CO_2 – the assigned values for ethanol are based on results from 3 instruments, 3 reagent lots, and 3 sample pools for a total of 9 test runs. Each run generates 5 replicates per calibrator level; 45 total replicates per level. The CO_2 assigned values for CHEM 3 CAL are the mean of a minimum of 30 replicates per level. Target ranges for CO_2 are 0 ± 5 mmol/L for Level A and 46 – 53 mmol/L for Level B.

Ethyl Alcohol – the assigned values for ethanol are based on results from 3 instruments, 3 reagent lots, and 3 sample pools for a total of 9 runs. Each run generates 5 replicates per calibrator level; 45 total replicates per level. The ethyl alcohol assigned values for CHEM 3 CAL Levels A and B are the mean of a minimum of 30 replicates per level. Target ranges for ethanol are 0 ± 3 mg/dL for Level A and 307- 322 mg/dL for Level B.

d. *Detection limit:*

The LoB, LoD, and LoQ were evaluated in accordance with CLSI EP17-A. LoQ is defined as the value where inter-assay imprecision <20% CV. The table below summarizes the protocol and provides the value for each limit.

Limit	Protocol	Value
LoB	4 blank samples were tested for 3 days, 1 run per day, 2 replicates per run, 2 reagent lots, 1 instrument	4 µg/dL
LoD	4 low level ammonia samples were tested for 3 days, 1 run per day, 2 replicates per run, 2 reagent lots, 1 instrument	15 µg/dL
LoQ	3 low level samples diluted with purified water were tested for 3 days, 1 run per day, 3 replicates per run, 2 reagent lots, 1 instrument	17 µg/dL

e. Analytical specificity:

The AMM method was evaluated for interference according to CLSI EP7-A2 guideline. Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10% is considered significant interference. Testing was performed with two ammonia levels (85 and 426 µg/dL). The following substances do not cause significant interference (>10% bias) with the AMM method when present in serum at the concentrations indicated.

Interferent	**Test concentration mg/dL**
Acetaminophen	20
Amikacin	8
Ampicillin	5.
Ascorbic acid	6
Caffeine	6
Carbamazepine	3
Cefoxitine	0.3
Chloramphenicol	5
Chlordiazepoxide	1
Chlorpromazine	0.2
Cimetidine	2
Diazepam	0.5
Digoxin	0.61
Erythromycin	6
Ethanol	600
Ethosuximide	25
Furosemide	6
Gentamicin	1
Heparin	3.0 U/mL
Ibuprofen	50
Lidocaine	1.2
Lithium	2.2
Nicotine	0.1
Penicillin G	25 U/mL
Pentobarbital	8
Phenobarbital	10
Phenytoin	5
Primidone	4
Propoxyphene	0.16
Protein, Total	14,000
Salicylic acid	60

Theophylline	4
Urea	500
Valproic acid	50
Vancomycin	10

For Hemolysis, Icterus, and Lipemia (HIL) Interferences:

Substance Tested	**Substance Concentration**	**Ammonia concentration (µg/dL)**	**Bias (%)**
Hemoglobin (hemolysate)	75 mg/dL 500 mg/dL	85 426	+12 +17
Bilirubin (unconjugated)	80 mg/dL 80 mg/dL	85 426	< 10 < 10
Bilirubin (conjugated)	60 mg/dL 80 mg/dL	85 426	-16 < 10
Lipemia (Intralipid®)	50 mg/dL 50 mg/dL	85 426	+ 13 < 10

The sponsor has the following limitations stated in the package insert:

Do not use hemolyzed samples. Bilirubin (conjugated) at 60 mg/dL decreases ammonia results by 16% at ammonia concentration of 85 µg/dL. Lipemia (Intralipid) at 50 mg/dL increases ammonia results by 13% at ammonia concentration of 85 µg/dL.

For some endogenous substances, the sponsor performed a dose-response study to evaluate interference using real patient sample pools that contained the interference substances. Non-significant interference was defined by having the observed recovery within 10% of expected value. The following substances did not cause >10% recovery at the concentrations tested.

Substance Tested	**Test concentration**	**Ammonia Concentration** (µg/dL)
Albumin	5.4 g/dL	182
Cholesterol	364 mg/dL	232
Creatinine	31.1 mg/dL	233
Immunoglobulin G	3.4 g/dL	308
Triglyceride	1102 mg/dL	354
Uric Acid	9.3 mg/dL	196

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed between the Siemens Dimension Vista® Ammonia (AMM) assay and the predicate Siemens Dimension® Ammonia (AMON) method following the CLSI EP9-A2 guideline.

For this study, 100 excess, de-identified lithium heparin plasma samples containing measurable amounts of ammonia and were purchased from multiple vendors as well as supplemented by normal samples collected in-house and tested at an internal site. Samples were run in duplicate and the first replicate was used in the data analysis. The range of ammonia values in the comparison study was 19 - 1273 µg/dL. Least squares linear regression was performed and the results of the regression are summarized below.

Device	Predicate	Slope	Intercept	Correlation Coefficient (r)	n
Dimension Vista® AMM	Dimension ® AMON	1.03	13.6	0.993	100

b. Matrix comparison:

To demonstrate equivalency between lithium heparin plasma and EDTA plasma for Dimension Vista® AMM, comparison testing of 49 fresh matched lithium heparin and EDTA plasma samples was tested on the Dimension Vista® System. Samples were run in duplicate and the first replicate was used to compare AMM lithium heparin plasma versus EDTA plasma. The range of values in the comparison study was 39 - 1085 µg/dL. Least squares linear regression was used as the statistical method in the analysis of the data.

Lithium Heparin Plasma vs.	Slope	Intercept	Correlation Coefficient (r)	n
EDTA plasma	0.96	3.3	1.00	49

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Expected Values: 19- 54 µg/dL[1]

[1]The literature reference used was the *Textbook of Clinical Chemistry by NW Tietz; WB Saunders Co., Philadelphia, PA; pages 1487-1488*.

The reference interval of 19- 54 µg/dL was also validated for use with the Dimension Vista® Ammonia (AMM) assay by transference following CLSI C28-A3. The sponsor performed a validation study using 30 healthy adults (15 male and 15 female) to confirm the reference interval.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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