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

A. 510(k) Number:

k112142

B. Purpose for Submission:

New device

C. Measurand:

Lithium

D. Type of Test:

Quantitative colorimetry

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

Dimension Vista® Lithium (LITH) Flex® Reagent Cartridge

Dimension Vista® Drug 4 Calibrator

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NDW	II	21 CFR §862.3560 Lithium test system	Toxicology (81)
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 LITH method is an *in vitro* diagnostic test for the quantitative measurement of lithium in human serum and plasma on the Dimension Vista® System.

   Measurements of lithium are used to assure that the proper drug dosage is administered in the treatment of patients with mental disturbances, such as manic-depressive illness (bipolar disorder).

   The Drug 4 Calibrator is an *in vitro* diagnostic product for the calibration of the LOCI Digoxin (DIGXN) and Lithium (LITH) methods on the Dimension Vista® System.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Dimension Vista System. The 510(k) demonstrates assay performance on the Dimension Vista 1500.

I. Device Description:

Reagent components of the LITH method are shown in the table below:

Reagents wells	Form	Ingredients
1-6	Liquid	Dye, Diethylene glycol monoethyl ether 2(3)-tert-Butyl-4-hydroxyanisole, Surfactant Preservative
7-12	Liquid	KOH, Diethylene glycol monoethyl ether, Surfactant

The Drug 4 Calibrator is a five level liquid calibrator. The matrix is drug free normal human serum. Targets for the lithium levels are 0.0, 0.9, 1.8, 3.6, and 5.5 mmol/L. The calibrator was previously cleared for Digoxin (k093441).

Each donor unit used in the preparation of this product was tested by FDA-approved methods for the presence of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2), as well as for Hepatitis B Surface Antigen (HBsAg) and antibody to Hepatitis C Virus (HCV), and found to be negative (not repeatedly reactive).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension® Lithium (LI) Flex® Reagent Cartridge

   Dimension® Drug Calibrator

2. Predicate K number(s):

   k011033, k011035

3. Comparison with predicate:

Assay:

Similarities		
Item	Proposed Device	Predicate Device (k011033)
Intended use	Is an *in vitro* diagnostic test for the quantitative measurement of lithium in human serum and plasma.	Same
Indications for use	Measurements of lithium are used to assure that the proper drug dosage is administered in the treatment of patients with mental disturbances, such as manic-depressive illness (bipolar disorder).	Same
Sample Types	Serum and Sodium Heparin Plasma	Same

Differences		
Item	Proposed Device	Predicate Device (k011033)
Measuring Range	0.20 – 3.00 mmol/L	0.20 - 5.00 mmol/L
Sample size	2 uL	10 uL
Bichromatic endpoints	510 and 700 nm	540 and 700 nm

Calibrator:

Similarities		
Item	Proposed Device	Predicate Device (k011035)
Intended use/ Indications for use	An *in vitro* diagnostic product for the calibration of the Lithium (LITH) and other methods on the Dimension Vista® System.	Same
Matrix	Human serum	Same
Preparation	Liquid; ready to use	Same
Storage	2 - 8˚C	Same

Differences		
Item	Proposed Device	Predicate Device (k011035)
Analytes	Lithium and Digoxin	Lithium, Digoxin, Phenobarbital, Phenytoin, and Theophylline

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

- CLSI Guideline EP5-A2: *Evaluation of Precision Performance of Quantitative Measurement Methods*
- CLSI Guideline EP 17-A: *Protocols for Determination of Limits of Detection and Limits of Quantitation*
- CLSI Guideline EP6-A: *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*
- CLSI Guideline EP9-A2*: Method Comparison and Bias Estimation Using Patient Samples*
- CLSI Protocol EP7-A2: *Interference Testing in Clinical Chemistry*

L. Test Principle:

The LITH method employs a lithium-specific chromoionophore that forms a complex with the Li^+ ion in an alkaline solution.

Li^+ + Lithium Dye → Dye-Li Complex (absorbs at 510 nm)

The concentration of lithium in the sample is proportional to the increase in absorbance, which is due to the formation of the dye-lithium complex. The reaction is measured using a bichromatic (510 and 700 nm) endpoint technique.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision testing for the LITH method was performed over twenty days according to CLSI EP5-A2. Test samples consisted of two levels of a commercially available control, two serum pools and one plasma (Na+ heparin) pool. The two serum pools and one plasma pool were spiked with lithium carbonate. On each day of testing, each sample was run in duplicate, in two separate runs. Testing was performed over 20 days, two separate runs

with two test samples for each test material. The studies included one Flex lot, one instrument and one calibrator lot.

The range of samples spans the analytical measurement range. Analysis of variance (ANOVA) was used to evaluate the data consistent with recommendations of EP5-A2.

Sample		Mean (mmol /L)	Repeatability		Within-lab	
			SD	% CV	SD	% CV
Controls	Level 1	0.86	0.01	1.7	0.02	2.5
	Level 2	1.67	0.02	1.1	0.03	1.6
Serum pool	Level 1	0.67	0.01	1.9	0.03	4.9
	Level 2	2.48	0.03	1.2	0.07	2.7
Plasma pool	Level 1	1.24	0.02	1.4	0.03	2.7

b. Linearity/assay reportable range:

The linear range was determined according to CLSI EP6-A. Based on the results of this study and that from the Limit of Detection study, the analytical measuring range was established. The LITH measuring range is 0.20 - 3.00 mmol/L.

The linearity study covered the range of 0.00 to 3.16 mmol/L for serum and 0.02 to 3.22 mmol/L for plasma (Na+ heparin). Linearity testing was performed using human serum and plasma pools spiked with lithium carbonate and then diluted for intermediate levels by sequential mixing with drug-free serum and/or plasma. For each sample type, nine samples were prepared by sequential mixing and analyzed in N=5 replicates.

The expected values listed in the tables below are based on dilutions of a standard solution of known concentration.

The predicted values from the most statistically significant polynomial regressions were compared to the predicted values from the linear regressions and the bias was calculated for each level.

Plasma:

Sample	Expected value	Observed value	Predicted linear	Predicted Quadratic	Bias	
					mmol/L	%
L1	0.00	0.02	0.02	0.01	-0.01	n/a
L2	0.41	0.41	0.43	0.42	0.00	-0.6
L3	0.82	0.83	0.83	0.83	0.00	0.4
L4	1.23	1.24	1.23	1.24	0.01	0.5
L5	1.64	1.65	1.63	1.64	0.01	0.5
L6	2.04	2.03	2.02	2.03	0.01	0.3
L7	2.45	2.43	2.43	2.43	0.00	0.1
L8	2.86	2.82	2.83	2.82	0.00	-0.1
L9	3.27	3.22	3.23	3.22	-0.01	-0.3

Linear regression analysis:

$y = 0.9795x + 0.0257$
$R^2 = 0.9999$

Serum:

Sample	Expected value	Observed value	Predicted linear	Predicted Cubic	Bias	
					mmol/L	%
L1	0.00	-0.03	0.00	-0.03	-0.02	n/a
L2	0.40	0.39	0.40	0.40	0.00	0.0
L3	0.80	0.81	0.79	0.81	0.01	1.4
L4	1.19	1.19	1.18	1.20	0.01	1.2
L5	1.59	1.61	1.58	1.59	0.01	0.7
L6	1.99	1.98	1.98	1.99	0.00	0.2
L7	2.39	2.38	2.38	2.38	0.00	-0.1
L8	2.78	2.79	2.77	2.76	-0.01	-0.3
L9	3.18	3.16	3.17	3.16	-0.01	-0.2

Linear regression analysis:

$y = 0.998x - 0.0031$

$R^2 = 0.9997$

Recovery: A recovery study was also performed. Samples were each independently volumetrically prepared using a highly concentrated lithium stock solution, and expected values are calculated based upon the amount of lithium carbonate added to each sample. In addition, a control is prepared for each sample by spiking the diluent used to prepare the lithium carbonate stock solution (in this case, water) into the sample matrix. Recovery is determined relative to control for each sample.

Serum results:

Expected (mmol/L)	Observed (mmol/L)		% Recovery
	Test	Control	
0.00	-0.03	n/a	n/a
0.60	0.58	-0.03	101%
1.20	1.14	-0.05	99%
1.80	1.75	-0.04	99%
2.40	2.34	-0.03	99%
3.00	2.93	-0.04	99%

Plasma results:

Expected (mmol/L)	Observed (mmol/L)		% Recovery
	Test	Control	
0.00	0.02	n/a	n/a
0.60	0.66	0.03	105%
1.20	1.20	0.02	98%
1.80	1.78	0.02	98%
2.40	2.36	0.02	97%
3.00	2.96	0.02	98%

Out of range specimens (with results in excess of 3.00 mmol/L) are to be manually diluted. Autodilution is not recommended.

Samples with results less than 0.20 mmol/L will be reported as "less than 0.20 mmol/L" by the instrument.

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

Traceability: The calibrator is traceable to NIST SRM1 924. It is a liquid human serum base product containing lithium packaged as two vials for each of five levels. Level A is drug free normal human serum and Levels B - E contain lithium carbonate material in human serum.

Value assignment: The four levels of Lithium master pool are manufactured by weighing in the appropriate amount of NIST SRM 924 Lithium reference material into drug free normal human serum. (Level 1 does not contain analyte and has a concentration of 0.0 mmol/L.) Each Masterpool level is tested on Dimension for content verification against a previous masterpool and current calibrator lot. The estimated uncertainties in the assigned values of calibrator material range from 0.4 to 0.7%.

Commercial calibrator lots are produced by adding lithium gravimetrically to drug free normal human serum. Values are assigned to each lot of calibrator from the Lithium master pool using multiple instruments and reagent lots.

Stability: The calibrators are stable until the expiration date printed on the vial when stored unopened and opened at 2-8 ˚C.

Real time stability studies are ongoing for unopened, opened and punctured calibrators. The sponsor also evaluated three freeze-thaws. Stability testing protocols were presented in the 510(k) and sponsor's acceptance criteria were reviewed and found to be acceptable.

d. Detection limit:

The sponsor followed CLSI Guideline EP 17-A: *Protocols for Determination of Limits of Detection and Limits of Quantitation* to determine the Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ).

Five lithium free samples (five independent lots of Calibrator Level A (zero level)) and five low level samples (serum samples spiked with lithium carbonate) were tested for three days, one run per day, two replicates per run, with two reagent lots, on two instruments. Calibration of both instruments was performed using the same lot of calibrator and all testing was performed by the same operator.

The Limit of Blank (LoB) for LITH was determined to be 0.05 mmol/L and the Limit of Detection (LoD) for LITH was determined to be 0.08 mmol/L.

In order to establish the Limit of Quantitation (LoQ) four unique patient samples were gravimetrically prepared to 0.15 mmol/L lithium using NIST SRM 924a Lithium Carbonate. Two instruments were used and two lots of reagents (a different reagent lot per instrument). Each of the four samples were processed in triplicate during each run. Three runs were performed on each instrument system (one run per day). A total of 72 measurements were obtained. The mean observed sample concentration was 0.158 mmol/L, with overall bias (relative to the concentration based on the standard) of 0.008 mmol/L. The %CV at 0.158 mmol/L was 8.5%, and a Total Analytical Error (TAE) of 0.035 mmol/L was determined. Consistent with this, the sponsor has set the lower limit of the claimed measuring range to be 0.20 mmol/L. Samples with results less than 0.20 mmol/L will be reported as "less than 0.20 mmol/L" by the instrument.

e. Analytical specificity:

Interference testing was performed according to CLSI Guideline EP7-A2 to determine the effect of various endogenous and exogenous substances on the LITH assay. For all interferents the percent bias was determined by testing a control sample without the interferent and comparing it to the value obtained from a test sample to which the potential interferent had been added.

Test samples were prepared by spiking the potential interferent into serum spiked with lithium carbonate. Testing was performed at LITH concentrations

of approximately 0.60 mmol/L and 1.50 mmol/L. The low level of 0.60 mmol/L was chosen based upon its medical relevance as the lower limit of the therapeutic range. The upper level of 1.50 mmol/L was chosen based upon CLSI Guideline EP7-A2.

Interference testing was performed with one lot of reagents. Five replicates were tested for each substance.

Significant interference was defined as a bias of >0.10 mmol/L for the low LITH sample and >10% bias for the high LITH sample relative to the control sample.

Interference was evaluated at several levels of potential interferent for the following compounds:

Interferent	Amount	Amount (SI units)	Bias at 0.60 mmol/L LITH	Bias at 1.5 mmol/L LITH
Bilirubin (conjugated)	20 mg/dL	342 µmol/L	0.13 mmol/L	11%
	15 mg/dL	256 µmol/L	0.10 mmol/L	8%
	10 mg/dL	171 µmol/L	0.07 mmol/L	5%
	5 mg/dL	86 µmol/L	0.03 mmol/L	3%
	2 mg/dL	34 µmol/L	0.00 mmol/L	-1%
	1 mg/dL	17 µmol/L	0.01 mmol/L	-1%
Bilirubin (unconjugated)	20 mg/dL	342 µmol/L	0.18 mmol/L	14%
	15 mg/dL	256 µmol/L	0.14 mmol/L	10%
	10 mg/dL	171 µmol/L	0.10 mmol/L	6%
	5 mg/dL	86 µmol/L	0.04 mmol/L	2%
	2 mg/dL	34 µmol/L	0.02 mmol/L	4%
	1 mg/dL	17 µmol/L	-0.01 mmol/L	0%
Hemoglobin	500 mg/dL	0.32 mmol/L	0.21 mmol/L	18%
	300 mg/dL	0.19 mmol/L	0.11 mmol/L	11%
	200 mg/dL	0.13 mmol/L	0.10 mmol/L	7%
	100 mg/dL	0.06 mmol/L	0.07 mmol/L	4%
	50 mg/dL	0.03 mmol/L	0.01 mmol/L	1%
	25 mg/dL	0.02 mmol/L	0.01 mmol/L	3%

The package insert indicates the following levels of endogenous compounds do not cause interference (defined as bias less than 0.10 mmol/L or 10% at lithium concentrations 0.60 and 1.50 mmol/L, respectively):

Substance tested	Concentration
Hemoglobin(hemolysate)	200 mg/dL
Bilirubin, unconjugated	10 mg/dL
Bilirubin, conjugated	15 mg/dL
Lipemia (Intralipid)	3000 mg/dL

The sponsor indicates in their package insert that “Hemolyzed specimens should not be used with this assay.”

Interference was not detected for the following compounds:

Substance	Test Concentration	SI Units
Acetaminophen	20 mg/dL	1324 µmol/L
Amikacin	8.0 mg/dL	137 µmol/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic Acid	6.0 mg/dL	342 µmol/L
Caffeine	6.0 mg/dL	308 µmol/L
Calcium	25 mg/dL	6.3 mmol/L
Carbamazepine	3.0 mg/dL	127 µmol/L
Chloramphenicol	5.0 mg/dL	155 µmol/L
Chlordiazepoxide	1.0 mg/dL	33.3 µmol/L
Chlorpromazine	0.2 mg/dL	6.27 µmol/L
Cholesterol	503 mg/dL	13 mmol/L
Cimetidine	2.0 mg/dL	79.2 µmol/L
Copper	1588 µg/dL	250 µmol/L
Creatinine	30 mg/dL	2.65 mmol/L
Dextran 40	6000 mg/dL	1500 µmol/L
Diazepam	0.51 mg/dL	18 µmol/L
Digoxin	6.1 ng/mL	7.8 nmol/L
Erythromycin	6.0 mg/dL	81.6 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25.0 mg/dL	1770 µmol/L
Furosemide	6.0 mg/dL	181 µmol/L
Gentamicin	1.0 mg/dL	21 µmol/L
Heparin	3.0 U/mL	3000 U/L
Ibuprofen	50.0 mg/dL	2425 µmol/L
Immunoglobulin G (IgG)	5000 mg/dL	50 g/L
Intralipid	3000 mg/dL	30 g/L
Iron	1117 µg/dL	200 µmol/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Magnesium	10.5 mg/dL	4.3 mmol/L
Nicotine	0.10 mg/dL	6.2 µmol/L
Penicillin G	25 U/mL	25,000 U/L
Pentobarbital	8.0 mg/dL	354 µmol/L
Phenobarbital	10.0 mg/dL	431 µmol/L
Phenytoin	5.0 mg/dL	198 µmol/L
Potassium	8.0 mmol/L	8.0 mmol/L
Primidone	4.0 mg/dL	183 µmol/L
Propoxyphene	0.16 mg/dL	4.91 µmol/L

Protein: Albumin	6000 mg/dL	60 g/L
Protein: Total	12,000 mg/dL	120 g/L
Salicylic Acid	60 mg/dL	4.34 mmol/L
Sodium	200 mmol/L	200 mmol/L
Theophylline	4.0 mg/dL	222 µmol/L
Urea	500 mg/dL	83 mmol/L
Uric Acid	20 mg/dL	1.2 mmol/L
Valproic Acid	50 mg/dL	3467 µmol/L
Vancomycin	10 mg/dL	69 µmol/L
Zinc	1625 µg/dL	250 µmol/L

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The predicate device used to demonstrate substantial equivalence to the Dimension Vista LITH assay is the Dimension LI Assay for the Dimension Clinical Chemistry System previously cleared under k011033. The method comparison study included 104 excess, de-identified serum samples and 40 excess de-identified Na^+ Heparin plasma samples containing measurable amounts of lithium within the analytical measurement range of the DV LITH assay. Testing was performed over 9 days by two operators at one site. One instrument and one lot of calibrators and reagents were used.

Passing Bablock Regression Statistics:
N = 144
Slope = 0.957 95% CI: 0.956, 0.957
Intercept = 0.04 mmol/L 95% CI: 0.04, 0.04
r = 0.997
Sy,x = 0.05 mmol/L
Range = 0.23 - 2.91 mmol/L

b. Matrix comparison:

Matched serum and Na+ heparin plasma samples were collected from patients and donors and tested on the Dimension Vista System with the Dimension Vista LITH assay. Both fresh and frozen samples were analyzed.

Spiked samples were prepared by adding aqueous lithium carbonate to freshly drawn matched sets of serum and Na+ heparin plasma from healthy donors. Sample spikes were made such that the lithium carbonate stock solution contributed to no more than 2% of the final sample matrix.

LITH values were determined with the Dimension Vista LITH assay. Samples were run in duplicate and the first replicate was used to compare LITH in plasma versus serum by Passing-Bablock regression analysis.

Comparison of 55 matched undiluted serum and Na+ heparin plasma samples on the Dimension Vista System gave the following statistics using Passing-Bablock regression:

Slope: 1.01
Intercept: -0.02 mmol/L
N: 55
r: 0.997
Range: 0.32 - 2.93 mmol/L

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:

   The therapeutic range of 0.60 - 1.20 mmol/L. is obtained from the literature (see below).

   The following is included in the package insert:

   Therapeutic lithium concentrations vary significantly, depending on the individual. A therapeutic range of 0.60 to 1.20 mmol/L includes effective serum/plasma concentrations for many patients; however, some individuals are best treated at concentrations outside this range.[1,2,3]

   Concentrations of 1.20 to 1.50 mmol/L signify a warning range, and a concentration in excess of 1.50 mmol/L in a specimen drawn 12 hours after the dose indicates a significant risk of intoxication.[1]

   Concentrations greater than 2.00 mmol/L are often associated with toxic symptoms.[1,2,3]

Note: The physician must ultimately determine the most appropriate lithium therapeutic range for each patient.

1. Burtis CA, Ashwood ER. Tietz Fundamentals of Clinical Chemistry, Fifth Edition, W.B. Saunders Company, Philadelphia, PA 2001: pp. 1023.
2. Kaplan LA, Pesce AJ. Clinical Chemistry: Theory, analysis, and correlation, Fourth Edition, Mosby, Inc., St. Louis, MO 2003; pp. 1085.
3. Baselt RC, Cravey RH. Disposition of Toxic Drugs and Chemicals in Man, Fourth Edition, Chemical Toxicology Institute, Foster City, CA 1995; pp. 430.

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.