

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

A. 510(k) Number:

k063705

B. Purpose for Submission:

New device

C. Measurand:

Lithium, Theophylline

D. Type of Test:

Quantitative Ion Selective Electrode (Li⁺)

Quantitative Enzyme Immunoassay

E. Applicant:

Thermo Fisher Scientific Oy

F. Proprietary and Established Names:

Lithium (Li⁺) Micro Volume Electrode

Theophylline

G. Regulatory Information:

1. Regulation section:

21 CFR § 862.3560 Lithium test system

21 CFR § 862.3880 Theophylline test system

21 CFR § 862.1150 Calibrator

21 CFR § 862.3200 Clinical toxicology calibrator

2. Classification:

Class II

3. Product code:

NDW, KLS, JIX, DKB

4. Panel:

Chemistry (75); Toxicology (91)

H. Intended Use:

1. Intended uses:

See Indications for use below.

2. Indications for use:

Lithium is intended for *in vitro* diagnostic use in the quantitative determination of the lithium concentration in human serum on T60 Clinical Chemistry Analyzers. Measurements are used as an aid in the management of individuals taking lithium for the treatment of mental disturbances, such as manic-depressive illness (bipolar disorder).

Theophylline is intended for quantitative in-vitro diagnostic determination of the theophylline concentration in human serum using T60 Clinical Chemistry Analyzers. Measurements are used in the diagnosis and treatment of theophylline overdose and in monitoring levels of theophylline to ensure proper therapy.

The ISE Calibrators 1 and 2 & 3 are intended for calibration of ion selective electrodes for quantitative measurements of potassium, sodium and chloride in human serum or plasma and lithium in human serum. For the in vitro diagnostic use on the T60 analyzer.

TDM Calibration set B is intended for in vitro diagnostic use as a calibrator in the quantitative measurement of the kit code 981649 Theophylline assay on T60 Analyzer.

3. Special conditions for use statement:
For prescription use only.
4. Special instrument requirements:
Siemens T60 and T60i, Siemens T60i Kusti

I. Device Description:

The Lithium Micro Volume Electrode (Li^+) is packed in a foil bag.

Theophylline assay:

- a. Reagent A buffer (enzyme acceptor reconstitution buffer: MOPS (3-(N-morpholino)propane sulfonic acid buffer), mouse monoclonal anti-theophylline antibodies and sodium azide (less than 1%))
- b. Reagent A lyophilizate (enzyme acceptor reagent: enzyme acceptor (microbial) 0.171 g/l, buffer salts and sodium azide (less than 1%))
- c. Reagent B buffer (enzyme donor reconstitution buffer: MES (2-(N-morpholino)ethanesulfonic acid buffer), and sodium azide (less than 1%))
- d. Reagent B lyophilizate (enzyme donor (microbial) conjugated to theophylline 0.06 mg/l, chlorophenol red- β -D-galactopyranoside 1.64 g/l, theophylline 0.38 mg/l, and sodium azide (less than 1%)).

ISE Calibrators 1 and 2&3: ready-for-use aqueous liquid solutions which contain purified chemicals (NaCl, KCl, CH_3COONa , MgCl_2 , CaCl_2 , LiCl) buffer and preservative. The ISE Calibrator 1 is provided in a foil bag and the ISE Calibrators 2&3 are provided in plastic bottles.

TDM Calibrator Set B: ready-for-use aqueous liquid solutions which contain buffer salts, bovine serum albumin and sodium azide (< 0.15%). TDM Calibrator B1 contains theophylline. Both TDM calibrator B0 and calibrator B1 are provided in vials (7.5 ml and 5.0 ml, respectively).

J. Substantial Equivalence Information:

1. Predicate device names:
Infinity Lithium Reagent for Olympus
Thermo TRACE Lithium Reagent and Lithium Standard (Calibrators only)
CEDIA Theophylline Assay

CEDIA Core TDM Multi-Cal

2. Predicate 510(k) numbers:
k003583, k961462, k961659
3. Comparison with predicate:

Lithium:

Similarities		
	Predicate device (k003583)	Proposed device
Intended use	Quantitative determination of the lithium concentration	Same
Traceability of calibrators	NIST SRM 924	Same

Differences		
	Predicate device (k003583)	Proposed device
Test principle	Spectrophotometric	Potentiometric
Matrix type	Serum and EDTA-plasma	Serum
Instrument	Olympus AU400	T60, DPC T60i, DPC T60i Kusti
Measuring range	0.04 – 3.00 mmol/l	0.2 – 4.0 mmol/l

Theophylline:

Similarities		
	Predicate device (k961462)	Proposed device
Indications for Use	Measurements are used in the diagnosis and treatment of theophylline overdose and in monitoring levels of theophylline to ensure proper therapy.	same
Test principle	Homogeneous enzyme immunoassay system	same
Traceability of calibrators	The calibration values are traceable to USP reference materials prepared gravimetrically to drug-free human serum.	same

Differences		
	Predicate device (k961462)	Proposed device
Matrix type	Serum or plasma (Na or Li heparin, Na EDTA)	Serum
Instrument	Roche Hitachi 911/917	Siemens T60, T60i, T60i Kusti
Measuring range	0.8 – 40 µg/ml	1.4 – 40 µg/ml

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

CLSI Documents:

- *User Evaluation of Precision Performance of Clinical Chemistry Devices: Approved Guideline (EP5-A2)*
- *Evaluation of the Linearity of Quantitative Measurement Procedures: a Statistical Approach: Approved Guideline (EP6-A2)*
- *Interference Testing in Clinical Chemistry: Approved Guideline (EP7-A2)*
- *Method Comparison and Bias Estimation using Patient Samples: Approved Guideline (EP9-A2)*

L. Test Principle:

Electrolyte measurements in the T60 analyzer are made with ion selective electrodes (ISE) directly without any dilution of the sample. The measurement cell consists of several ion selective electrodes and one reference electrode. The measured potential between each ISE and the common reference electrode is in the simplest case related to the natural logarithm of the ionic activity according to the Nernst equation. The changes in potential are developed across the ISE membrane/sample interface. Selectivity coefficients toward other ions must be known in the determination of lithium, as the lithium electrode is also sensitive to sodium. This is taken into account in the Nikolsky equation.

The theophylline assay uses recombinant DNA technology to produce a unique homogeneous enzyme immunoassay system. The assay is based on the bacterial enzyme β -galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociate to form fully active enzyme that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotometrically. In the assay, analyte in the sample competes with analyte conjugated to one inactive fragment of β -galactosidase for antibody binding site. If analyte is present in the sample, it binds to antibody, leaving the inactive enzyme fragments free to form active enzyme. If analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the reassociation of inactive β -galactosidase fragments, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of drug present in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Lithium: To evaluate precision, the within-run and between-run repeatability of the Lithium assay was calculated using CLSI EP5-A2 as a guideline. Two commercially marketed serum controls were measured on two runs per day, two replicates per run, over 21 days (low control sample) or 22 days (high control) using three T60 analyzers, three electrodes and two operators.

Theophylline: The within-run and between-run repeatability as well as total precision of the Theophylline assay was calculated using CLSI EP5-A2 as a guideline. Three commercially marketed controls (sub-therapeutic, therapeutic and toxic levels) were tested over 21 days, two runs per day, two replicates per run, two reagent lots, by three operators, on three different instruments.

Assay	Mean	Total		Between run		Within run	
		SD	CV (%)	SD	CV (%)	SD	CV (%)
Li	0.95 mmol/L	0.020	2.1	0.009	0.9	0.008	0.9
Li	1.86 mmol/L	0.039	2.1	0.009	0.5	0.017	0.9
Theo	4.4 µg/ml	0.35	8.0	0.10	2.2	0.17	3.9
Theo	13.8 µg/ml	0.59	4.3	0.18	1.3	0.21	1.5
Theo	28.1 µg/ml	0.87	3.1	0.31	1.1	0.21	0.8

b. Linearity/assay reportable range:

Lithium: The claimed measuring range is 0.2 - 4.0 mmol/l. Linearity across the range was evaluated with a dilution series using normal level human serum spiked with lithium chloride with values spanning the measuring range. Four parallel measurements were made in random order. The assay recovered +/- 0.15 mmol/l or +/- 10% from expected values.

Theophylline: The claimed measuring range is 1.4 – 40 µg/ml. Linearity across the range was evaluated with two studies. The first study used the low and high calibrator (TDM Calibrator B0 and B1) to create a series of 11 samples that ranged from 0.283 – 44.8 µg/ml. The second dilution series used low patient serum spiked with TDM Calibrator B1 and samples ranged from 1.0 – 49 µg/ml. Four parallel measurements were made in random order for both dilution series. Both series showed recovery within +/- 10% from expected values.

It is recommended in the labeling that samples with theophylline values above 40 µg/ml are diluted 1:1 with the TDM Calibrator 0 before re-testing. This recommendation was tested by preparing 1-to-1 dilutions with TDM Calibrator B0 as well as drug free serum and comparing recovery with the expected value. The high samples were prepared by spiking separate low level human serum samples with TDM Calibrator B1. The spiked serum samples were then diluted 1- to-1 both with drug free serum and with TDM calibrator B0. The four replicates of the diluted samples were analyzed on the T60 analyzer. Dilution of high sample with TDM Calibrator B0 showed efficient recovery of all samples tested.

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

ISE Calibrator 1 and 2&3: The ISE Calibrators are prepared gravimetrically using purity grade chemicals and purified laboratory water. The levels of the calibrators are verified by comparison to the in-house reference lot, which is traceable to the primary NIST standard SMR 924 using the reference

measurement procedure, in this case NBR 260-69. The most recent traceability testing was performed by DGKL (Reference Institute of the German Society of Clinical Chemistry and Laboratory Medicine, Germany). To test the normal production lots of a new ISE Calibrators the ion-selective electrode-based electrolyte analyzer is calibrated with the manufacturer's ISE Standards. Control sera are used to verify the calibration and electrode functionality. The ISE Calibrator lots to be checked are then measured alongside the existing ISE Standards five times each interspersed with the serum controls to check the consistency of the calibration.

Shelf life (2°C) and on-board stability testing protocols and the acceptance criteria for stability testing were described and found to be acceptable.

TDM Calibrator Set B: The primary standard is prepared gravimetrically from mixing USP Theophylline reference material into drug-free human serum. Value assignment of new lots of primary standards (high and low) is verified through validation studies using the previous set of primary standards. Commercial product calibrators are made with Theophylline in an artificial matrix. The commercial calibrators are assigned values based on the current set of primary calibrators (1 vial x 10 determinations each, 3 runs).

Shelf life (2-8°C) and open vial (60 days at 2-8°C) stability testing protocols and the acceptance criteria for stability testing were described and found to be acceptable.

d. Detection limit:

Theophylline: Limit of Blank (LoB) was determined with 24 replicates of TDM Calibrator B0 solution. The LoB was defined as the concentration corresponding to three standard deviations above the average concentration, and calculated to be 0.8 µg/mL. The Limit of Detection (LoD) was determined to be 1.4 µg/mL.

The low detection limit of the Lithium ISE electrode (0.2 mmol/L) was validated in the linearity study described above.

e. Analytical specificity:

Interference studies: An evaluation of potential assay interferences was performed to assess the performance of the Lithium and Theophylline assays when potential contaminants are present in a sample. Testing was done according to CLSI EP7-A2. Non-interference was defined as deviations less than or equal to ± 10% of the initial value.

Lithium: No interference was found with bilirubin (total) up to 40 mg/dl, hemolysis up to 1000 mg/dl or lipemia up to 1000 mg/dl.

The following substances were screened at (or above) the CLSI document EP7-A or Laboratory Handbook¹ suggested screening concentrations in three levels of Li⁺ (0.5, 1.2, 2.0 mM). The Li⁺ concentrations in the patient sera (Scipac) were spiked from a 0.5 M stock LiCl solution. The following table lists the substances tested and the screen concentrations used:

Substance	Concentration
Acetaminophen	253.50 µg/mL
Acetazolamide	30.67 µg/mL
Acetylsalicylic Acid (aspirin)	612.54 µg/mL
Calcium (ionized)	14.84 mg/dL
Carbamazepine	30.01 µg/mL
Copper	984.96 µg/dL
Ibuprofen	499.63 µg/mL
Iron	563.58 µg/dL
Magnesium (ionized)	4.862 mg/dL
Methyl Paraben	160.00 mg/dL
N-Acetylprocainamide	39.94 µg/dL
Phenobarbital	102.67 µg/dL
Phenytoin (5,5-Diphenylhydantoin)	50.50 µg/dL
Potassium	10.3 mmol/L
Procainamide	24.00 µg/dL
Quinidine	12.88 µg/dL
Sodium	200 mmol/L
Theophylline	40.00 µg/dL
Valproate	496.48 µg/dL
Zinc	771.60 µg/dL

Samples containing the interferant were compared against blank samples. If the results varied by more than 5% or by more than 0.05 mmol/L, the substance was considered to interfere with the Li⁺ test. Of these 20 species, only methyl paraben was a significant interferant towards the T60i Li⁺ ISE measurement, and caused a decrease in the measured Li⁺ concentration. A series of 5 concentrations was then run for the Li⁺ method with methyl paraben as the interferant to determine what concentration of methyl paraben does not interfere significantly, and it was determined that methyl paraben levels as low as 39 mg/dL can cause a 5% decrease in the measured Li⁺.

Li ⁺ Level	Bias with 150 mg/dL methyl paraben	% Bias
0.5 mmol/L	- 0.084 mmol/L	16.80%
1.2 mmol/L	- 0.198 mmol/L	16.50%

¹ Jacobs, David S., DeMott, W.R., Oxley, D.K. *Laboratory Test Handbook CONCISE with Disease Index*, 3rd Edition, 2004, LEXI-COMP, Hudson, OH.

2.1 mmol/L - 0.298 mmol/L 14.19%

Theophylline: No interference was found for bilirubin (total) up to 58.5 mg/dl, hemolysis up to 1000 mg/dl or lipemia up to 1000 mg/dl. Acetaminophen, ephedrine, and epinephrine were also screened for potential interference. No interference was found for Acetaminophen up to 520 µg/ml, Ephedrine up to 25 µg/ml, and Epinephrine up to 20 µg/ml. Additional compounds were tested for cross-reactivity (see product insert). Cross-reactivity with 1,3-Dimethyluric acid was seen and a note in the assay labeling indicates that uremic patients should not be evaluated with this assay.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed as recommended in CLSI document EP9-A.

Lithium: The Thermo Fisher Scientific Oy Lithium Micro Volume Electrode on the DPC T60 analyzer was compared to the Infinity Lithium reagent on the Olympus AU400 System. 104 patient serum samples and 12 spiked serum samples ranging from 0.25 – 4.09 mmol/L were tested.

$$y = 0.984x - 0.010$$

$$r = 0.999$$

Theophylline: The Thermo Fisher Scientific Oy Theophylline assay on the DPC T60 analyzer was compared to the Microgenics CEDIA II Theophylline assay on the Hitachi 911/917 analyzer. 131 patient serum samples and 11 spiked serum samples were tested ranging from 1.1 - 37.7 µg/ml. Nine sample results were excluded because the results were below the range (1.4 µg/ml) for the proposed device.

$$y = 0.989x + 0.05$$

$$r = 0.998$$

b. Matrix comparison:
Not applicable.

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:

Lithium: Therapeutic levels: 0.6 – 1.2 mmol/l. Concentrations of 1.2 to 1.5 mmol/l signify a warning range and concentrations over 1.5 mmol/l indicate a significant risk of intoxication. See Tietz N. W. Fundamentals of Clinical Chemistry 4th edition, WB Saunders Co., Philadelphia, PA; 1996; 402-426.

Theophylline: According to different sources, the suggested therapeutic ranges are:

8 – 20 ug/ml or 44 - 111 mmol/l (Asthma)^{1,2}

10 - 20 ug/ml or 56 - 111 mmol/l (Asthma)³

5 – 10 ug/ml or 28 – 56 mmol/l (Apnea)¹

¹ Tietz N. W. Fundamentals of Clinical Chemistry 4th edition, WB Saunders Co., Philadelphia, PA; 1996; 402-426.

² Clinical Laboratory Diagnostics; Use and Assessment of Clinical Laboratory Results, 1st edition, TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, Germany; 1998; 1145-1157.

³ Disposition of Toxic Drugs and Chemicals in Man, 3rd edition, Year Book Medical Publishers, Inc., Chicago, IL; 1990; 789-793.

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.