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

A. 510(k) Number:

k063684

B. Purpose for Submission:

New assay and addition of lithium to an already cleared calibrator.

C. Measurand:

Lithium

D. Type of Test:

Quantitative

E. Applicant:

Roche Diagnostics Corp.

F. Proprietary and Established Names:

Cobas Lithium

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NDW	II	21 CFR 862.3530	Chemistry
JIX	II	21 CFR 862.1150	Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   In vitro test for the quantitative determination of lithium in human serum and plasma on Roche/Hitachi Cobas C systems. Measurements of lithium are used as an aid in the management of patients taking lithium for the treatment of mental

disturbances such as manic- depressive illness (bipolar disorder).

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Roche/Hitachi Cobas Systems

I. Device Description:

The Roche Cobas Lithium assay is a ready to use reagent consisting of sodium hydroxide, EDTA, substituted porphyrin, preservatives and detergent. The device uses the multi-analyte calibrator (k990460, k033501 and k062319) for automated systems (C.f.a.s.) and the sponsor recommends using the Precinorm/Precipath U and Precinorm/Precipath U plus control materials.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Integra ISE Direct

2. Predicate K number(s):

   k963627

3. Comparison with predicate:

The predicate for this device is the Roche Integra ISE Direct (k963527) and the similarities and differences are noted below.

Similarities	**Proposed device**	**Predicate (k963627)**
Intended Use	See above	Same
Matrix	Serum and Plasma	Serum and Plasma
Differences	**Proposed device**	**Predicate (k963627)**
Range	0.05 mMol/L to 3.00 mMol/L (to 6.0 mMol/L with autodilution feature)	0.25 mMol/L to 1.9 mMol/L
Method	Colorimetric	Ion Selective Electrode
Instrument	Roche Cobas	Roche Integra

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

GUIDANCE			
Document Title	**Office**	**Division**	**Web Page**
Points to Consider Guidance Document on Assayed and Unassayed Quality Control Material	OIVD		http://www.fda.gov/cdrh/ode/99.html

L. Test Principle:

The Cobas lithium is a colorimetric test in which lithium present in a sample reacts with a substituted porphyrin compound at an alkaline pH, resulting in a change in absorbance which is directly proportional to the concentration of lithium in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Imprecision was evaluated for 21 days by testing two serum samples and two controls in triplicates on the Cobas c501 analyzer on a single lot at the manufacturer's site. Within-run precision was evaluated by testing two serum samples and two controls in replicates of 21 on the Cobas c501 analyzer on a single lot. The results are shown in the table below.

Within-Run				
Sample material	Low control (mMol/l)	High control (mMol/l)	Low serum (mMol/l)	High serum (mMol/l)
Days	1	1	1	1
N	21	21	21	21
Mean	0.77	2.38	0.46	1.40
SD	0.01	0.02	0.01	0.02
CV	1.7	1.0	1.9	1.2
"Total"				
Sample material	Low control (mMol/l)	High control (mMol/l)	Low serum (mMol/l)	High serum (mMol/l)
Days	21	21	21	21
N	63	63	63	63
Mean	0.79	2.42	0.64	1.62
SD	0.02	0.03	0.01	0.03
CV	2.17	1.28	2.33	1.56

b. Linearity/assay reportable range:

The sponsor conducted two recovery studies to encompass the following ranges- 0.01 to 1.03 mMol/l and 0.00 to 3.37 mMol/l. The dilution series (11 samples) were prepared from spiked lithium chloride serum samples and the recovered values were compared to the theoretical values based on known dilutions. The deviations from expected recovery for the assay ranged from 90.9 to 104.4%.

The sponsor validated the upper auto-dilution range via a recovery study using automated dilution rerun 5 samples ranging from 3.51 to 5.66 mMol/l. The control material was run in duplicate and the percent recovery ranged from 99% to 104%.

The combined results supports the sponsor's claimed measuring range of 0.05 mMol/l to 3.00 mMol/l (up to 6.00 mMol/l with autodilution).

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

The sponsor conducted shelf-life and on-board reagent stability studies and the results supports the sponsor's shelf life stability claim of 12 months and an on-board stability claim of 4 weeks.

The sponsor also conducted a shelf-life stability study on the C.f.a.s. calibrators. The results support the calibrators 24 month stability claim.

The C.f.a.s. lithium values are traceable to SEM 956b, a serum-based lithium standard reference material.

d. Detection limit:

The sponsor conducted a limit of blank (LoB) study according CLSI EP 17-A. Five human sera samples free of analyte were measured in duplicate in six separate runs for a total of 60 values. The sponsor reports a LoB of 0.02 mMol/L.

The sponsor conducted as limit of detection (LoD) study according to guidelines CLSI EP 17-A. The LoD was determined as the lowest amount of analyte in a sample that can be detected with 95% probability. Five samples with low lithium concentrations between 0.1 and 0.5 mMol/L were measured in duplicate in six separate runs for a total of 60 values. The precision (SD) was calculated for each sample. A pooled estimate of precision over the five samples was then determined (SDtotal) and the LOD was calculated as LoD=LoB + 1.653 x SDtotal. The sponsor reports a LoD of 0.05 mMol/L.

Precision at the lower assay range was determined by evaluating ten samples with concentrations ranging from 0 and 0.4 mMol/L, twice a day over 5 days on the Cobas c01 analyzer. The mean, standard deviation and the CV were calculated for each concentration and the CVs were plotted against the mean concentration. Based on this evaluation and the linearity evaluation, the lowest concentration where the CV yielded 20% or less was 0.09 mMol/L.

e. Analytical specificity:

Endogenous interferents were tested using pooled human plasma and serum samples spiked with varying levels of interferent. The samples were tested in triplicates and the median values were used to calculate recovery. Five different human serum/plasma pools containing 0.82 – 1.10 mMol/L lithium were tested for hemoglobin, bilirubin and intralipid interference. Ten levels of hemoglobin were tested up to 1000 mg/dL. Eleven levels of conjugated and unconjugated bilirubin were tested up to 61.0 mg/dL. Ten levels of intralipid were tested up to 2000 mg/dL. The sponsor defined interference as recovery greater than +/-10% of initial values at therapeutic concentrations. There was no interference detected up to the concentrations noted above.

Eighteen commonly used pharmaceuticals were tested for interference with the lithium test system. Two serum pools with two lithium concentrations (0.91 and 1.48 mMol/L) were tested. Varying concentrations of interferent were added and samples were analyzed in triplicate. The sponsor defined interference as recovery greater than +/-5% of initial values at therapeutic concentrations. No interference was detected at the concentrations tested. The following drugs were tested:

Acetylcystein	Ampicillin-Na	Axcorbic acid	Ca-Dobesilate	Cyclosporine	Na-Cefoxitin
Lithium Heparin	Intralipid	Levodopa	Methydopa+1,5	Metronidazole	Phenylbutazone
Doxycyclin (tetracycline)	Acetylsalycilic acid	Rifampicin	Acetaminophen	Ibuprofin	Theophilline

Eight potentially interfering cations were studied for interference with the lithium test system (0.91 and 0.94 mMol/L). The interfering compounds were weighed in gravimetrically and no interference was observed for any of the compounds up to the concentrations listed below.

NH4Cl (19.8 µmol/L)	NaCl (140 Mol/L)	KCl (4 mMol/L) 1.01	CaCl2 (2.4 mMol/L)
MgCl2 (0.9 mMol/L)	FeCl3 (1.04 mg(L)	Cu(NO3)2 (1.15 mMol/L)	ZnCl2 (1.07 mMol/L)

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The sponsor conducted a method comparison study compared to the predicate. Seventy eight unaltered patient samples ranging from 0.120 to 3.345 mMol/l were run against a commercially available reagent. The results for both the Passing/Bablok and least squares regression are shown below.

	Passing/ Bablok	Least Squares
N	77	77
Range (mMol/L)	0.120- 3.0	0.120 – 3.0
Slope	0.992	0.962
Y intercept	0.034	0.0604
R	0.957 (Kendall)	0.9979 (Pearson)

b. Matrix comparison:

The sponsor conducted most of the studies for this submission on serum samples. To validate the use of additional sample types (sodium heparin and potassium EDTA plasma and serum separator tubes (SST)) parallel samples were collected in serum, SST, Na-Heparin plasma and K_2 EDTA plasma tubes. Samples were collected from 20 different donors. Lithium was spiked to all tubes resulting in a lithium concentrations ranging from 0.6 to 1.75 mMol/L. Two anticoagulant concentrations were assessed for each type of anticoagulant with serum clot activator tube as the reference. Each sample was split and 20 were filled completely and 20 were half-filled resulting in twice the expected anticoagulant concentration. Plasma results were compared to the serum results and percent recovery was determined. The percentage deviations from expected recovery for the assay ranged from 95.5 to 102.6 for SST, 95.5 to 102.9 for filled sodium heparin, 95.0 to 104.4 for half-filled sodium heparin, 94.3 to 105.6 for the filled K2-EDTA and 94.4 to 105.6 for half-filled K2-EDTA. The results support the usage of SST, sodium heparin and potassium EDTA with the device.

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 sponsor references the following ranges for lithium expected values:

Therapeutic concentration 0.6- 1.2 mMol/L

Toxic Range > 2.0 mMol/L

"Reference Values for Therapeutic and Toxic Drugs: Tietz Fundamentals of Clinical Chemistry, Fifth Edition, Edited by Burtis CA, Ashwood ER, WB Saunders Company, 2001"

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.