

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

A. 510(k) Number:

k090282

B. Analyte:

Lidocaine

C. Type of Test:

Turbidimetric immunoassay

D. Applicant:

Thermo Fisher Scientific Inc.,

E. Proprietary and Established Names:

QMS Lidocaine

F. Regulatory Information:

1. Regulation section: 21 CFR 862.3555
2. Classification: Class II
3. Product code: KLR
4. Panel: Toxicology

H. Intended Use:

1. Intended use(s):

The QMS Lidocaine Immunoassay is intended for the quantitative determination of lidocaine in human serum or plasma on automated clinical chemistry analyzers. The results obtained are used in the diagnosis and treatment of lidocaine overdose and in monitoring levels of lidocaine to help ensure appropriate therapy.

2. Indication(s) for use:

See Intended use above.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

The assay has been validated by the manufacturer on the Hitachi 717.

I. Device Description:

The QMS Lidocaine Immunoassay assay consists of the packaged reagents (R1 and R2):

The R1 Antibody Reagent includes

Anti-lidocaine Mouse Monoclonal Antibody and <0.1% sodium azide as preservative.

The R2 Microparticles include

Lidocaine-coated Microparticles and <0.1% sodium azide as preservative.

This product contains human sourced and/or potentially infectious components. Components sourced from human blood have been tested by FDA-approved methods and found to be nonreactive for HBsAg, anti-HIV 1/2, and anti-HCV.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Roche ONLINE TDM Lidocaine Assay

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

k032334

3. Comparison with predicate:

The assays have the same indications for use, and use the same technology and reagents. Both assays are for use on automated analyzers.

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

CLSI document:

“Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline-Second Edition (EP05-A2).

L. Test Principle:

The assay is a homogeneous particle-enhanced turbidimetric assay, based on antibody-binding competition between drug in the sample and microparticle-bound drug. Antibody binding causes microparticle agglutination. The rate of absorbance, measured spectrophotometrically, is proportional to the rate of agglutination.

M. Performance Characteristics (if/when applicable):

Performance was validated on the Hitachi 717 instrument, using the Roche Preciset TDM calibrators (A-F) (k031856) and the Roche TDM Control Set (k060429).

1. Analytical performance:

a. Precision

Precision was performed in-house, using the protocol described in CLSI EP5-A2. Commercially available tri-level human serum control set (k060429) containing lidocaine was assayed in duplicate, twice a day for 20 non-consecutive days on one analyzer, by one operator, using one reagent and calibrator lot. Each control sample was tested for a total of 80 replicates. Calibration was performed initially and re-calibration was performed at the day 10 data point. Results are summarized below.

			Within Run		Between Day		Total	
Control	N	Mean (µg/ml)	SD (ug/mL)	%CV	SD (ug/mL)	%CV	SD (ug/mL)	%CV
Low	80	1.76	0.10	5.66	0.10	5.41	0.14	8.13
Mid	80	4.42	0.15	3.48	0.11	2.44	0.22	5.06
High	80	8.83	0.24	2.73	0.19	2.17	0.46	5.27

b. Linearity/assay reportable range:

Recovery was determined by spiking lidocaine into human serum negative for the drug to achieve concentrations across the assay range. The theoretical concentration of lidocaine (in the table below) was determined gravimetrically. The average of replicates measured with the QMS reagents were used to determine mean recovery. Results are shown below.

Theoretical Conc. (µg/mL)	Mean Recovered Conc. (µg/mL)	% Recovery
9.33	8.57	91.9
4.67	4.29	91.9
2.33	2.12	91.0

Additional linearity and recovery studies across the claimed assay range (0.75 to 10 µg/mL) were performed by diluting commercially available serum based calibrator (up to 10.0 µg/mL) with drug-free or lower concentration calibrators. These studies and the limit of quantitation study below supported the claimed assay range of 0.8 to 10 µg/mL. The percent recovery across the range of the assay observed in these studies was 93 - 99%.

Results of linear regression analysis were:

Slope: 0.961

Intercept: -0.04

R²= 0.9968

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

Controls and calibrators were previously cleared (k060429 and k031856) and are sold separately.

d. *Detection limit:*

A patient pool with a lidocaine value of 0.93 µg/mL was diluted with normal human serum negative for lidocaine to give the following theoretical values: 0.154, 0.309, 0.463, 0.617, and 0.771 µg/mL. Each level was assayed twice a day for 5 days. The mean concentration, the standard deviation and the coefficient of variations (CV) were calculated. In addition, recovery studies with calibrator-derived samples containing concentrations of lidocaine near the assay lower limit, demonstrated recovery within 93-95% relative to theoretical calibrator-derived concentrations. The limit of quantitation was determined to be 0.8 ug/mL, where the assay has a CV less than 20% and recovery is within +/- 10% (see table below for data):

mean measured sample concentration (µg/mL)	0.79	0.93
SD (µg/mL)	0.107	0.094
% CV	13.58%	10.17%

e. *Analytical specificity:*

Cross-Reactivity:

The assay was evaluated for potential interference from the N-ethylglycyl-2,6-xylidide (MEGX) and glycyl-2,6-xylidide (GX), the two major *in vivo* metabolites produced by the liver. Metabolites of >99% purity were spiked at 10 times the highest known concentrations of each into a human serum control containing lidocaine at a concentration of approximately 4 µg/ml. Control samples contained the same concentration of lidocaine, with no metabolite. Percent cross reactivity for metabolites and drugs were defined as $[(Da-Dt)/C] \times 100$, where Dt = the measured concentration of the control analyte, Da = measured concentration of the control analyte + cross-reactant and C = known concentration cross reactant. Calculated cross-reactivities are based on the median of triplicate determinations. Less than 1% cross-reactivity was observed for the MEGX and GX.

Endogenous Compounds:

To evaluate interference from endogenous compounds, a series of dilutions containing varying levels of the endogenous compounds was prepared from spiked and negative serum pools. Testing was done in the presence of 5-7

µg/ml lidocaine (except for human anti-mouse antibodies (HAMA) testing, in which samples contained ~5 µg/ml lidocaine). Percent recovery was calculated relative to control samples containing lidocaine without spiked endogenous compounds. The mean observed concentration was used in calculation of recovery. The following is a summary of the obtained data.

Endogenous Substance tested	Endogenous substance Concentration	N	Target (No Interferent) µg/mL	Mean Observed Recovery µg/mL	% Recovery
Bilirubin	15 mg/dL	2	7.25	6.63	91.4
Hemoglobin	10 g/L	2	5.28	5.37	102.0
Triglyceride	2000 mg/dL	3	5.24	5.12	97.84
Rheumatoid Factor	1500 IU	3	5.21	5.13	98.53
Total protein	1-12 g/dL	3	5.90	6.00	103

A normal human serum pool (control), and HAMA type 1 and HAMA type 2 samples was spiked with the same amounts of lidocaine. Each of the samples was assayed in duplicate. Results are shown in the table below. As with any assay employing mouse antibodies, the possibility exists for interference by HAMA in the sample, which could cause falsely elevated results.

	Rep 1 (µg/mL)	Rep 2 (µg/mL)	Mean Recovery (µg/mL)	SD	CV	% Recovery
Control	4.47	4.24	4.36	0.163	3.7	-
HAMA Type-1	4.08	3.98	4.03	0.071	1.8	92.0
HAMA Type-2	4.02	4.03	4.03	0.007	0.2	92.0

Thirty-six common drugs and compounds were tested for interference. Results are shown below. ND indicates not detectable. Cross-reactivity of < 1% was considered ND.

Compound	Concentration Tested (µg/mL)	% Cross- Reactivity
Mepivacaine	10	63
Bupivacaine	40	20
Acetaminophen	200	ND
Acetyl Cysteine	1660	ND
Acetylsalicylic acid	650	ND
Ampicillin-Na	53	ND
Asorbic Acid	60	ND
Cefoxitin	660	ND
Cyclosporine	0.5	ND
Digoxin	0.01	ND
Disopyramide	10	ND
d-Methamphetamine	10	ND
Ephedrine	0.1	ND
Flecainide	10	ND
Furosemide	60	ND
Hydrochlorothiazide	6	ND
Ibuprofen	500	ND
Isoproterenol	0.01	ND
Levodopa	80	ND
Lidocaine-N-ethyl Bromide	100	ND
Methylodopa+1,5	15	ND
Metronidazole	120	ND
Mexiletine	100	ND
Phenybutazone	100	ND
Phenytoin (DPH)	50	ND
PPX (L-Pipecolic acid-2,6- xylidide)	10	3.4
Procainamide	24	ND
Propanolol	2.0	ND
Quinidine	12	ND
Rifampicin	64	ND
Tetracycline	15	ND
Theophylline	40	ND
Tocainide	100	1.0

ND = Not Detectable

f. Assay cut-off:

Not applicable

2. Comparison studies: (outliers, repeat measurements, graphs)

a. *Method comparison with predicate device:*

Results obtained with the QMS Lidocaine Assay were compared to those obtained with the same serum and plasma samples using the Roche Lidocaine assay. No other specific criteria (in terms of patient demographics) were applied in sample selection. 52 samples were evaluated by the QMS assay on a Hitachi 717 analyzer in accordance with the procedure described in the proposed package insert. Single measurements for each method were used in the analysis. The samples ranged in concentration on the Hitachi 717 from 1.11 µg/mL to 9.38 µg/mL.

Results of Passing-Bablok analysis were:

Slope: 1.076 [1.044 to 1.104]

Intercept: -0.096 [-0.153 to -0.024]

R = 0.993

R² = 0.986

b. *Matrix comparison:*

Recovery studies for serum and plasma samples were performed using blood in various collection tubes from healthy volunteers, including: serum/glass tube; no additive, serum with clot activator, lithium heparin tube, sodium heparin tube and K2 EDTA tube. The serum or plasma was spiked with four different concentrations of lidocaine (1.8 µg/mL, 5 µg/mL, 8 µg/mL and 10 µg/mL). Samples were analyzed on day 0, 3 and 7. The percent recovery of lidocaine in serum and plasma was within +/-97.50 or better. In addition, samples containing high concentration of anticoagulants were spiked and tested with lidocaine at 1.8, 5 and 8 ug/mL. The results showed no interference with the QMS Lidocaine assay.

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 manufacturer includes the following in the package insert:

“The therapeutic range for total concentration is stated as 1.5 to 6 ug/mL.”*

“Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.”

* Burtis CA, et. al. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. Elsevier Saunders; 2006:1259.

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 substantial equivalence decision.