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

A. 510(k) Number:

k122766

B. Purpose for Submission:

Modification to indications to include liver transplant patients.

C. Measurand:

Everolimus

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Microgenics Corporation, Thermo Fisher Scientific, Clinical Diagnostics Division

F. Proprietary and Established Names:

Thermo Scientific QMS® Everolimus Assay

G. Regulatory Information:

1. Regulation section: CFR §862.3840, Sirolimus Test System
2. Classification: Class II
3. Product code: OUF
4. Panel: Toxicology (91)

H. Intended Use:

1. Intended use(s):
   See indications for use.
2. Indication(s) for use:
   The QMS® Everolimus Assay is intended for the quantitative determination of Everolimus, in human whole blood on automated clinical chemistry analyzers.

The results obtained are used as an aid in the management of kidney and liver transplant patients receiving Everolimus therapy. This in vitro diagnostic device is intended for clinical laboratory use only.

3. Special conditions for use statement(s):

For prescription use.

See expected values section, below. The manufacturer also includes the following in the package insert.

In addition, the manufacturer includes the following in the package insert:
On average, the assay is designed so that bias for patient samples relative to LC-MS/MS systems is within 0 to ±10%. However, as with other immunosuppressant immunoassays, caution should be exercised because results for individual patient samples may vary (in a positive or negative direction) due to the difference in metabolite accumulation or other errors.

The assay should not be used for patients who have recently been administered sirolimus (until sirolimus parent compound and metabolites are fully cleared) since the assay cross-reacts with sirolimus and its metabolites.

Certain conditions that can affect the parent compound to metabolite ratio in patient samples may affect performance (e.g. bias relative to an LC-MS/MS assay). For such patients, consider confirming results with an LC-MS/MS method specific for the parent compound.

Test findings should always be assessed in conjunction with the patient's medical history, clinical examinations and other findings.

4. Special instrument requirements:

Performance was evaluated on the Hitachi 917.

I. Device Description:

The QMS® Everolimus Assay consists of separately packaged reagents (R1, R2 and Precipitation Reagent).
R1: Everolimus Antibody Reagent: <1.0% Anti-Everolimus polyclonal antibody (rabbit) in a buffer as stabilizer and <0.09% sodium azide as preservative.
R2: <0.5% Everolimus-coated microparticles in buffer containing <0.09% sodium azide as preservative.

Calibrators and controls are supplied with the assay and have been previously cleared under k100144. Please see k100144 for a complete description of calibrators and controls.

J. Substantial Equivalence Information:

1. Predicate device name(s):

QMS® Everolimus Assay

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

k100144

3. Comparison with predicate:

The predicate and candidate device are the same physical device and are the same in terms of all manufacturing and technological characteristics. The new version of the device includes an additional indication for use as an aid in management of liver transplant patients receiving everolimus therapy.

Device	QMS Everolimus Assay (Candidate)	QMS Everolimus Assay k100144 (Predicate)
Indication(s) for use	Same (with the addition of liver transplant patients to the indication).	Intended for the quantitative determination of everolimus, in human whole blood on automated clinical chemistry analyzers. The results obtained are used as an aid in the management of kidney transplant patients receiving everolimus therapy
Assay principle	Same	See **Test Principle** below.
Assay reagents	Same	See **Device Description** above.

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

- CLSI EP-5, Evaluation of Precision Performance of Quantitative Measurement Methods.
- CLSI EP-7, Interference Testing in Clinical Chemistry.

L. Test Principle:

The QMS Everolimus Assay is a homogeneous particle-enhanced turbidimetric immunoassay based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the everolimus antibody reagent. The principle is based on everolimus-coated microparticle reagent agglutinating in the presence of the anti-everolimus antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically at a wavelength of 700 nm. When a sample containing everolimus is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest everolimus concentration and the lowest agglutination rate at the highest everolimus concentration.

M. Performance Characteristics (if/when applicable):

Performance was validated on the Hitachi 917.

1. Analytical performance:

a. Precision/Reproducibility:

Three levels of control samples containing everolimus and three patient sample pools (from liver transplant patients treated with everolimus) were assayed using two lots of QMS® everolimus reagents. Over 20 days, two individual aliquots from each sample assayed by QMS® Everolimus Assay, once in the morning and once in the afternoon. Each sample in the evaluation was extracted separately. Runs were separated by a minimum of two hours. Results are shown below.

Lot 1

Sample	Expected Value	Total N	Mean (ng/mL)	Within Run	Between Run	Total
Control Level 1	4.35	80	4.39	3.7%	4.0%	6.0%
Control Level 2	8.25	80	8.51	3.6%	0.7%	4.6%
Control Level 3	15.2	80	15.57	2.3%	1.1%	3.2%
Patient Pool 1	2.90	80	2.74	4.4%	4.9%	8.1%
Patient Pool 2	5.05	80	5.41	2.5%	3.0%	4.7%
Patient Pool 3	12.5	80	13.01	2.3%	0.3%	3.2%

Lot 2

Sample	Expected Value	Total N	Mean (ng/mL)	Within Run	Between Run	Total
Control Level 1	4.35	80	4.43	3.4%	3.1%	6.4%
Control Level 2	8.25	80	8.41	2.8%	1.9%	4.1%
Control Level 3	15.2	80	15.55	2.5%	0.8%	3.4%
Patient Pool 1	2.90	80	2.88	5.3%	3.6%	9.2%
Patient Pool 2	5.05	80	5.46	2.9%	1.0%	5.0%
Patient Pool 3	12.5	80	12.98	2.4%	0.6%	3.4%

Precision at external sites was presented within k100144.

b. Linearity/assay reportable range:

Linearity/recovery by dilution:

The claimed assay range is 2.0 to 20 ng/mL. Linearity studies were performed by diluting a high concentration liver transplant patient sample pool to produce samples with everolimus concentrations across the assay range. The dilutions were made with whole blood hemolysate. The theoretical concentrations were based on the high sample concentration determined by LC-MS/MS methods. The theoretical target concentrations were calculated by multiplying the high level sample concentration by the dilution factor. Samples were assayed by QMS® Everolimus Assay using two lots of reagents. Values shown below are the mean of 5 replicates for each lot.

Target Value LC-MS (ng/mL)	Reagent Lot 1		Reagent Lot 2	
	QMS Meas. (Mean, ng/mL)	% Recovery	QMS Meas. (Mean, ng/mL)	% Recovery
0	0.00	—	0.00	—
1.66	1.53	93%	1.49	90%
2.21	2.07	94%	1.98	90%
4.41	4.34	98%	4.11	93%
6.62	6.66	101%	6.34	96%
8.83	9.23	105%	9.00	102%
11.04	11.91	108%	11.90	108%
13.24	14.03	106%	14.43	109%
15.45	16.84	109%	16.73	108%
17.66	18.61	105%	19.22	109%
19.86	20.30	102%	20.69	104%
22.07	21.20	96%	22.06	100%

Linear regression equation for lot 1 and 2 respectively were y=1.061x-0.148; y=1.090x-0.375.

In addition, high concentration patient samples were diluted as described in the package insert instructions. Recoveries of all samples were within +/- 10% of expected values.

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

Calibrators and Controls were cleared under k100144. Please see k100144.

d. Detection limit:

The limit of quantitation was evaluated using a (liver transplant) patient pool with a low everolimus value was further diluted with normal human hemolysate to prepare samples at six levels near and below 2.0 ng/mL. Target values were determined using the LC-MS/MS system. Each LOQ level was assayed with duplicate measurements, twice a day for 5 days. All measurements were from separately extracted sample. Two reagent lots were assessed. Data demonstrated that at the claimed LoQ concentration of 2.0 ng/mL, the upper 95% confidence intervals were within 20% CV and +/-15% recovery.

Data supported the previous claimed LoQ of 2.0 ng/mL cleared under k100144.

e. Analytical specificity:

Interference and cross-reactivity were reviewed under k100144. Additional drugs were tested to further support the new 510(k). The following commonly co-administered drugs were tested: Sulfamethoxazole (to 0.525 mg/mL); Valganciclovir hydrochloride (to 0.036 mg/mL); Pantoprazole sodium (to 0.015 mg/mL); Trimethoprim (to 0.045 mg/mL). Three levels of everolimus samples were prepared by spiking everolimus into normal human hemolysate: 1) Drug-free (0 ng/mL everolimus), 2) Low level (2.6 ng/mL everolimus), and 3) Therapeutic level (6.0 ng/mL everolimus). The potentially interfering drugs were spiked into these hemolysate levels for the study.

Percent recoveries observed in this evaluation (based on test sample/ control sample concentration of everolimus) ranged within 101-107%.

f. Assay cut-off:

Not applicable – this is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed using 179 banked samples from 130 patients liver transplant patients. (No more than 2 samples per donor were included in this analysis and the two blood samples from single donors were drawn at a minimum of 7 days apart). Patient time post-transplant ranged mostly between 9-26 months. Co-administered drugs were largely tacrolimus and corticosteroids. Donor samples were measured by two LC-MS/MS Systems and by the QMS® Everolimus Assay using 2 lots of reagents on a Hitachi 917 clinical analyzer. The regression analysis below is based on single measurements per sample by each method. All samples were pre-dose except for a few of the samples closer to the assay upper limit. Regression results and bias analyses for this evaluation are shown in the table below. (Results supporting the indication for kidney transplant patients were reviewed under k100114).

Methods	N	Deming		Passing-Bablok		R
		Slope (95% CI)	Intercept (95% CI)	Slope (95% CI)	Intercept (95% CI)	
System 1 LC-MS/MS vs. QMS (Rgt Lot 2)	179	1.074 (1.031 to 1.116)	0.084 (-0.231 to 0.399)	1.074 (1.030 to 1.120)	0.055 (-0.234 to 0.315)	0.965
System 1 LC-MS/MS vs. QMS (Rgt Lot 3)	179	1.054 (1.018 to 1.089)	-0.152 (-0.417to 0.112)	1.047 (1.011 to 1.089)	-0.224 (-0.421 to -0.021)	0.974
System 2 LC-MS/MS vs. QMS (Rgt Lot 2)	179	1.044 (1.005 to 1.084)	0.379 (0.088 to 0.670)	1.078 (1.028 to 1.130)	0.161 (-0.157 to 0.414)	0.968
System 2 LC-MS/MS vs. QMS (Rgt Lot 3)	179	1.025 (0.991 to 1.060)	0.135 (-0.120 to 0.389)	1.058 (1.023 to 1.099)	-0.109 (-0.328 to 0.088)	0.974

	Avg Bias	Bias SD	Avg.% Bias	N
System 1 LC-MS/MS vs. QMS (Rgt Lot 2)	0.578	0.917	9%	179
System 1 LC-MS/MS vs. QMS (Rgt Lot 3)	0.208	0.772	3%	179
System 2 LC-MS/MS vs. QMS	0.672	0.872	10%	179

(Rgt Lot 2)				
System 2 LC-MS/MS vs. QMS (Rgt Lot 3)	0.302	0.763	5%	179

b Matrix comparison:

Not applicable. The assay is intended for use with EDTA whole blood only.

3. Clinical studies:

a. Clinical Sensitivity: Not applicable; Clinical sensitivity and specificity is not typically provided in 510(k)s for this type of assay.

b. Clinical specificity: Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable): Data regarding patient demographics and selection criteria were provided in the method comparison evaluation in the 510(k).

4. Clinical cut-off:

Not applicable; this is a quantitative assay.

5. Expected values/Reference range:

The following is stated in the package insert:

The recommended everolimus therapuetic range using an LC-MS/MS method is 3 to 8 ng/mL for pre-dose samples. See therapeutic drug monitoring information in the drug package insert.

The QMS Everolimus assay has been calibrated using a set of trough samples from adult renal transplant patients administered everolimus in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids, so that the average bias for this population across the assay range should be within ±10% of the LC-MS/MS system used. **However this may vary depending on the nature of the samples, individual metabolite concentrations and the specific assay used. Test findings should always be assessed in conjunction with the patient's medical history, clinical signs and symptoms and other laboratory parameters. Assay values cannot be used as the sole indicator for making changes in treatment regimen.**

Values obtained with different methods cannot be used interchangeably due to differences in methods and cross-reactivity with metabolites, nor should

correction factors be applied. Consistent use of the same assay for individual patients is strongly recommended.

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.