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

A. 510(k) Number:

k102772

B. Purpose for Submission:

New Device

C. Measurand:

Mycophenolic Acid

D. Type of Test:

Quantitative homogenous particle enhanced turbidimetric inhibition immunoassay (PETINIA)

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Siemens Dimension® Mycophenolic Acid Flex® reagent cartridge

Siemens Dimension® Mycophenolic Acid Calibrator

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
OAV	II, Sirolimus Test System (Classification Name)	862.3840	Toxicology
DLJ	II, Clinical Toxicology Calibrator	862.3200	Toxicology

H. Intended Use:

1. Intended use(s):

   See indication(s) for use below.

2. Indication(s) for use:

   The Dimension® Mycophenolic Acid Flex® reagent cartridge is an in vitro diagnostic test for the quantitative measurement of Mycophenolic acid (MPA) in human plasma on the Dimension® clinical chemistry system. Measurements of MPA are used as an aid in the management of mycophenolic acid therapy in renal, hepatic, and cardiac transplant patients.

   The Dimension® Mycophenolic Acid Calibrator is an in vitro diagnostic product for the calibration of the Mycophenolic Acid method on the Dimension® clinical chemistry system.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   For use with the Dimension RxL Max clinical chemistry system.

I. Device Description:

The Siemens Mycophenolic Acid assay consists of three in vitro diagnostic liquid reagents that are contained within the flex cartridge:

Particle Reagent: 5.0 mg/mL plus stabilizers and preservatives; Antibody Reagent: 0.100 mg/mL (mouse monoclonal) plus stabilizers and preservatives, and buffer

The MPAT calibrator is an aqueous bovine serum albumin (BSA) matrix product containing Mycophenolic acid.

J. Substantial Equivalence Information:

1. Predicate device name (s):

   Roche Total MPA assay for the COBAS INTEGRA system
   Roche Total MPA Calibrators for the COBAS INTEGRA system

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

   k063520

3. Comparison with predicate:

Similarities - Reagent		
Item	Proposed Device	Predicate
Feature	**Dimension® Mycophenolic Acid Flex® Reagent Cartridge**	**Roche Total MPA assay for the COBAS INTEGRA system**
Intended Use	Same	*in vitro* diagnostic use; quantitative measurement of Mycophenolic Acid as an aid in the management of MPA therapy in renal and cardiac transplant patients.

Differences - Reagent		
Item	Proposed Device	Predicate
Feature	**Dimension® Mycophenolic Acid Flex® Reagent Cartridge**	**Roche Total MPA assay for the COBAS INTEGRA system**
Sample Type	EDTA Plasma only	Serum, EDTA Plasma
Assay Range	0.2 – 30.0 µg/mL	0.4 - 15 µg/mL, extendable with post-dilution to 50 µg/mL
Technology	Homogenous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique with the MPA rate of aggregation inversely proportional to the MPA concentration in the sample.	Enzyme-mimicking assay with MPA concentration inversely proportional to the formation of NADH.
Detection	Bichromatic turbidimetric readings at 340 nm and 700 nm.	Spectrophotometric readings
Sample Size	5 µL	3 µL
Binding Protein	monoclonal mycophenolic acid specific antibody	None present

Similarities – Calibrator		
Item	Proposed Device	Predicate
Feature	**Dimension® Mycophenolic Acid Calibrator**	**Roche Total MPA Calibrators for the COBAS INTEGRA system**
Intended Use	for the calibration of the Mycophenolic Acid assay	Same
Analytes	MPA	Same
Traceable to:	Gravimetric preparation	Same
Form	Liquid, stored at 2-8°C	Same

Differences – Calibrator		
Item	Proposed Device	Predicate
Matrix	Bovine Serum Albumin	Human Serum
Volume	Vial containing Level 1 with 5.0 mL and Levels 2-5 have 2.0 mL per vial.	Levels A - F with 5.0 mL each and one vial of diluents (10.0 mL)
Levels	5 levels (0, 0.7, 2.3, 6.7, and 30.0 µg/mL)	6 levels (0, 1, 3, 5, 10, 15 µg/mL)

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

CLSI EP09-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

CLSI EP5-A: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation

L. Test Principle:

The methodology for the MPAT assay is based on a homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique, which uses a synthetic

particle-mycophenolic acid conjugate (PR) and monoclonal mycophenolic acid specific antibody (Ab). Mycophenolic acid present in the sample competes with mycophenolic acid on the particles for available antibody, thereby decreasing the rate of aggregation. Hence, the rate of aggregation is inversely proportional to the concentration of mycophenolic acid in the sample. The rate of aggregation is measured using bichromatic turbidimetric readings at 340 nm and 700 nm. The reaction can be represented as follows:

Mycophenolic acid + PR + Ab ————> PR-Ab complex + mycophenolic acid-Ab

(scatters light at 340 nm)

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision performance was evaluated at two external sites and at the manufacturer's facility.

At the external sites, three EDTA plasma pools were analyzed in duplicate, twice a day, for 20 non-consecutive days. Testing was conducted on two Dimension RxL Max instruments (one instrument/site) by two operators (one operator/site) and one reagent lot. Results were as follows:

External Site 1 Level 1 for n = 20 Plasma Pool L1

Grand mean		SD	% CV
1.0	Repeatability	0.05	4.9
	Between Run	0.03	3.3
	Between Day	0.02	2.1
	Within-Lab	0.06	6.2

External Site 1 Level 2 for n = 20 Plasma Pool L2

Grand mean		SD	% CV
7.9	Repeatability	0.2	2.2
	Between Run	0.3	3.5
	Between Day	0.0	0.0
	Within-Lab	0.3	3.9

External Site 2 Level 1 for n = 20 Plasma Pool L1

Grand mean		SD	% CV
0.9	Repeatability	0.05	5.5
	Between Run	0.00	0.0
	Between Day	0.03	3.0
	Within-Lab	0.05	6.0

External Site 2 Level 2 for n = 20 Plasma Pool L2

Grand mean		SD	% CV
7.4	Repeatability	0.19	2.5
	Between Run	0.20	2.7
	Between Day	0.00	0.0
	Within-Lab	0.27	3.6

External Site 2 Level 3 for n = 20 Plasma Pool L3

Grand mean		SD	% CV
25.52	Repeatability	0.82	3.2
	Between Run	0.10	0.4
	Between Day	0.30	1.2
	Within-Lab	0.88	3.4

At the internal sites, plasma pools and a commercial control were analyzed in duplicate, twice a day, for 20 non-consecutive days. Testing was conducted on one instrument by one operator on one reagent lot. The reagent lot was different than that used at the external sites. Results were as follows:

Internal site plasma pool 1

Grand mean		SD	% CV
0.44	Repeatability	0.04	10.2
	Between Run	0.03	5.7
	Between Day	0.00	0.0
	Within-Lab	0.05	11.7

Internal site plasma pool 2

Grand mean		SD	% CV
1.02	Repeatability	0.03	3.3
	Between Run	0.03	2.5
	Between Day	0.02	2.0
	Within-Lab	0.05	4.6

Internal site plasma pool 3

Grand mean		SD	% CV
7.48	Repeatability	0.14	1.9
	Between Run	0.04	0.5
	Between Day	0.02	0.2
	Within-Lab	0.15	2.0

Commercial Control

Grand mean		SD	% CV
11.70	Repeatability	0.21	1.8
	Between Run	0.12	1.0
	Between Day	0.15	1.3
	Within-Lab	0.29	2.5

Internal Site Plasma Pool 4

Grand mean		SD	% CV
25.41	Repeatability	0.66	2.6
	Between Run	0.13	0.5
	Between Day	0.00	0.0
	Within-Lab	0.68	2.7

b. Linearity/assay reportable range:

The claimed reportable range of the assay is 0.2 - 30.0 µg/mL. Linearity was determined across the range of the assay by diluting a high MPAT plasma pool with a low MPAT plasma pool to yield 13 concentrations covering and extending slightly above and below the assay measuring range. The initial low starting concentration was an EDTA plasma sample not containing MPAT and the initial high starting concentration was determined by spiking in a known amount of MPAT. Theoretical values below are based on the gravimetrically-determined spiked concentrations and the dilution factors. The mean of 5 measurements was compared to the theoretical values according to the dilution scheme. All recoveries were within ± 9 % as follows:

Sample Pool	Observed Mean (µg/mL)	Theoretical Value (µg/mL)	Bias µg/mL	(%) Recovery
1	0.02	n/a	n/a	n/a
2	0.22	0.22	0	100
3	0.49	0.53	-0.04	92.4
4	0.99	1.03	-0.04	96.1
5	1.98	2.03	-0.05	97.5
6	3.68	4.04	-0.36	91.1

7	8.1	8.05	0.05	100.6
8	12.24	12.06	0.18	101.5
9	16.74	16.07	0.67	104.2
10	20.56	20.09	0.47	102.3
11	24.08	24.1	-0.02	99.9
12	27.76	28.11	-0.35	98.8
13	32.12	n/a	n/a	n/a

Simple linear regression produced the following equation: $y = 1.00x + 0.00$.

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

Calibrator Traceability and Value Assignment

Calibrators are provided at 0, 0.7, 2.3, 6.7, and 30.0 µg/mL and are prepared in an aqueous bovine serum albumin (BSA) matrix. Each commercial lot of calibrator is traceable to a five-level Anchor Pool of MPA. The Anchor Pool is traceable to a gravimetric measurement of MPA (Pharmaceutical grade raw material). The sponsor estimates the uncertainty of assigned values of lot calibrators relative to the pharmaceutical grade material to be < 4%.

Commercial lot values for each level are assigned from Dimension instruments calibrated with Anchor Pool.

Calibrator Stability

The claimed shelf life (closed vial) for the calibrator is 12 months at 2-8° C. Shelf life is determined by comparing multiple replicates of the calibrator stored at 2-8°C with the same material stored at < -20°C. The method is calibrated each month with calibrator stored at < -20°C. The 2-8°C material values are recovered (as unknowns) versus the calibration. Recovery versus time is monitored and percent change over time is determined. The sponsor's protocols and acceptance criteria were reviewed and found to be acceptable.

The claimed open vial stability for the calibrator is 60 days at 2-8°C. Opened vial stability is determined as follows: Vials are opened on day zero. A quantity sufficient for a calibration is removed and the vials are recapped and stored at 2-8°C. These vials are tested on days 0, 33 and 61. Freshly opened vials are tested on days 33 and 61 for comparison. The sponsor's protocols and acceptance criteria were reviewed and found to be acceptable.

d. *Detection limit:*

Five samples were gravimetrically spiked to 0.2 µg/mL MPA analyte for analysis. Two instruments were used, with a different reagent lot on each

instrument. The five samples were processed in triplicate during each run. Three runs were performed on each instrument system over three days. The sponsor analyzed LoQ data consistent with CLSI EP17-A. Results were as follows:

Instrument 1

Bias of individual measurements relative to LC-MS ranged from - 0.07 µg/mL to + 0.07 µg/mL

CV: 12.5% at 0.2 µg/mL

Instrument 2

Bias of individual measurements relative to LC-MS ranged from - 0.07 µg/mL to + 0.05 µg/mL.

CV: 16.4% at 0.20 µg/mL

The LoQ was determined to be 0.2 µg/mL.

e. *Analytical specificity:*

Specificity studies were conducted for two MPA metabolites, MPA-acyl glucuronide (MPA-ag) and 7-O-MPA-β-glucuronide (MPAG), in addition to the pro-drug Mycophenolate Mofetil (MMF). The percent cross-reactivity was calculated as follows:

% Cross Reactivity = ((Measured Analyte - Control Analyte) / (Metabolite concentration) X 100.

Plasma Pool [MPA] (µg/mL)	Compound Added	Quantity Added (µg/mL)	MPAT Result (µg/mL)	% Cross-Reactivity
0.0	MMF	5	2.6	53%
0.0	MMF	25	13.2	53%

Plasma Pool [MPA] (µg/mL)	Compound Added	Quantity Added (µg/mL)	MPAT Result (µg/mL)	% Cross-Reactivity
0.0	MMF	50	25.9	52%
5.0	MMF	5	7.8	62%
5.0	MMF	25	18.2	54%
5.0	MMF	50	33.96	58%
0.0	MPAG	50	0.26	0.5%
0.0	MPAG	100	0.70	0.7%
0.0	MPAG	1000	6.32	0.6%
5.0	MPAG	50	5.28	0.4%
5.0	MPAG	100	5.66	0.8%
5.0	MPAG	1000	12.48	0.8%
0.0	MPA-ag	1.0	0.71	59.3%
0.0	MPA-ag	5.0	3.29	64.5%
0.0	MPA-ag	25.0	13.34	53.1%
5.0	MPA-ag	1.0	5.51	36.8%
5.0	MPA-ag	5.0	7.04	42.0%
5.0	MPA-ag	25.0	16.45	46.1%

Ninety-five exogenous substances and co-administered drugs and four endogenous substances were tested to the highest concentration expected. Test substances, in duplicate, were spiked into aliquots of EDTA plasma pools containing MPA (2 µg/mL and 5µg/mL) and analyzed by calculating the mean and percent recovery of MPA. These results are compared to control samples prepared without the test substance. The manufacturer defined interference as bias greater than 10%. None of the substances in the list below caused significant interference at the concentrations tested.

Substance	Test Concentration	SI Units
Acetaminophen	20 mg/dL	1324 µmol/L
Acyclovir	1000 µg/mL	4.44 mmol/L
Albuterol	1.0 mg/mL	4.18 mmol/L
Amikacin	8.0 mg/dL	137 µmol/L
Amphotericin B	100 µg/mL	108.2 µmol/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic Acid	6.0 mg/dL	341 µmol/L
Azathioprine	1.0 mg/mL	10.8 µmol/L
Caffeine	6.0 mg/dL	309 µmol/L
Carbamazepine	3.0 mg/dL	127 µmol/L
Cefaclor	1.0 mg/mL	2.59 mmol/L
Cefazolin	1.2 mg/mL	2.6 mmol/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	500 mg/dL	12.9 mmol/L
Cimetidine	2 mg/dL	79.4 µmol/L
Ciprofloxacin	40 µg/mL	121 µmol/L
Clofibrate	0.25 mg/mL	1.03 mmol/L
Clonidine	0.5 mg/mL	1.88 mmol/L
Creatinine	30 mg/dL	2.65 mmol/L
Cyclosphosphamide	1.0 mg/mL	3.58 mmol/L
Cyclosporine	0.005 mg/mL	4.16 µmol/L
Dextran 40	6000 mg/dL	1500 µmol/L
Diazepam	0.5 mg/dL	18 µmol/L
Digoxin	6.1 ng/mL	7.8 nmol/L
Diphenhydramine	1.0 mg/mL	3.92 mmol/L
Disopyramide	1.0 mg/mL	2.94 mmol/L
Ephedrine	1.0 mg/mL	6.05 mmol/L
Erythromycin	6.0 mg/dL	81.7 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25.0 mg/dL	1.77 mmol/L
Everolimus	9.0 µg/mL	9.39 µmol/L
Fluconazole	100 µg/mL	326.8 µmol/L
Flucytosine	301 µg/mL	2.33 mmol/L
5-Fluorouracil	1.0 mg/mL	7.69 mmol/L
Furosemide	6.0 mg/dL	181 µmol/L
Gancyclovir	1100 µg/mL	3.97 mmol/L
Gentamicin	1.0 mg/dL	21 µmol/L
Griseofulvin	0.5 mg/mL	1.42 mmol/L
Heparin	3.0 U/mL	3000 U/L
Hydralazine	1.0 mg/mL	6.2 mmol/L
Hydrochlorothiazide	0.25 mg/mL	839 µmol/L
Ibuprofen	50.0 mg/dL	2.43 mmol/L
Immunoglobulin G	5 g/dL	50 g/L
Indomethacin	0.2 mg/mL	559 µmol/L
Isoniazid	1.0 mg/mL	7.30 mmol/L
Isoproterenol	0.25 mg/mL	1.18 mmol/L
Itraconazole	50 µg/mL	70.82 µmol/L
Kanamycin	1.0 mg/mL	1.72 mmol/L
Ketoconazole	100 µg/mL	188.2 µmol/L
Lidocaine	1.2 mg/dL	51.3 µmol/L
Lithium	2.2 mg/dL	3.2 mmol/L
Methicillin	0.5 mg/mL	1.24 mmol/L
Methotrexate	1.0 mg/mL	2.20 mmol/L
Methylprednisolone	1.0 mg/mL	2.67 mmol/L
Metoclopramide	1.0 mg/mL	2.97 mmol/L
Metoprolol	1.0 mg/mL	3.74 mmol/L
Miconazole	1.0 mg/mL	2.09 mmol/L
Nadolol	1.0 mg/mL	3.24 mmol/L

Naproxen	1.0 mg/mL	4.34 mmol/L
Neomycin	1.0 mg/mL	1.63 mmol/L
Niacin	1.0 mg/mL	8.13 mmol/L
Nicotine	0.10 mg/dL	6.2 µmol/L
Nifedipine	0.25 mg/mL	722 µmol/L
OKT3	6.0 µg/mL	6.0 mg/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
Phenylephrine	0.82 mg/mL	4.90 mmol/L
Phenytoin	5.0 mg/dL	198 µmol/L
Piperacillin	1.0 mg/mL	1.85 mmol/L
Prednisolone	0.25 mg/mL	693 µmol/L
Prednisone	0.25 mg/mL	697 µmol/L
Primidone	4.0 mg/dL	183 µmol/L
Probucol	0.2 mg/mL	387 µmol/L
Procainamide	1.0 mg/mL	3.67 mmol/L
Promethazine	1.0 mg/mL	3.12 mmol/L
Propanolol	0.22 mg/mL	845 µmol/L
Propoxyphene	0.16 mg/dL	4.91 µmol/L
Protein (Albumin)	4.7 g/dL	47 g/L
Protein (Total)	10.0 g/dL	100 g/L
Ranitidine	1.0 mg/mL	2.85 mmol/L
Rheumatoid Factor	489 IU/mL	489,000 IU/L
Rifampin	100 µg/mL	121.5 µmol/L
Salicylic Acid	60 mg/dL	4.34 mmol/L
Sirolimus	50 µg/mL	55.0 µmol/L
Streptomycin	1.0 mg/mL	1.7 mmol/L
Sulfaquinoxaline	1.0 mg/mL	3.10 mmol/L
Tacrolimus	0.0005 mg/mL	622 nmol/L
Theophylline	4.0 mg/dL	222 µmol/L
Tobramycin	100 µg/mL	213.9 µmol/L
Triamterene	1.0 mg/mL	3.95 mmol/L
Triglycerides	1000 mg/dL	11.3 mmol/L
Urea	500 mg/dL	83.3 mmol/L
Uric Acid	25 mg/dL	1.5 mmol/L
Valproic Acid	50 mg/dL	3.47 mmol/L
Vancomycin	614 µg/mL	424 µmol/L

A separate study was performed to asses the effect of hemoglobin, conjugated and unconjugated bilirubin, and triglycerides (through the use of Intralipid).

Test substances were prepared in duplicate; the interferent was added to EDTA plasma pools containing 2 µg/mL and 5 ug/mL of MPA. The samples were analyzed and the calculated mean of replicates and percent recovery of MPA were compared to the "negative control" (EDTA plasma pool with 2

µg/mL and 5 ug/mL of MPA without interferent). No interference was observed from these substances at the following levels:

Interferent	Concentration Tested
Hemoglobin	1000 mg/dL
Bilirubin (unconjugated)	80 mg/dL
Bilirubin (conjugated)	80 mg/dL
Triglycerides (Intralipid)	1000 mg/dL

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
The sponsor analyzed 109 EDTA plasma samples on the MPAT assay and on the HPLC reference method. These included 33 samples from liver transplant patients, 42 samples from kidney transplant patients, and 34 samples from heart transplant patients. All were clinical trough samples from adults. The concentration range of the samples was 0.2 – 29.7 µg/mL.

Deming regression including all sample types produced the following (with 95% Confidence Intervals):

slope: 1.04 (0.99 – 1.09)
y-int: -0.02 (-0.09 – 0.04)
r: 0.98
sy/x: 0.35

Deming regression for the individual sample types was as follows:

Heart

slope: 1.01 (0.93 to 1.10)
y-int: 0.0 (-0.03 to 0.04)
r: 0.97
sy/x: 0.21

Kidney

slope: 0.99 (0.92 to 1.06)
y-int: 0.17 (0.06 to 0.27)
r: 0.98
sy/x: 0.18

Liver

slope: 1.10 (0.91 to 1.29)
y-int: -0.07 (-0.17 to 0.03)
r: 0.99
sy/x: 0.59

b. Matrix comparison:

Not applicable. This assay is intended to be used with serum samples only.

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 optimal concentration range for mycophenolic acid in plasma or serum using this assay has not been established. Therefore in the labeling the sponsor states the following:

"Optimal concentration ranges vary according to the specific assay used, and therefore should be established for each specific assay. Values obtained with different assay methods should not be used interchangeably due to differences in cross-reactivity with metabolites, nor should correction factors be applied. Laboratories should include identification of the assay used in order to aid in interpretation of results. Each institution should establish the optimal ranges based on the specific assay used and other factors relevant to their patient population.

Optimal ranges depend upon the patient's clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of mycophenolic acid, co-administration of other immunosuppressants, time post-transplant and a number of other factors. Therefore, individual mycophenolic acid values cannot be used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimens are made.

Decreased incidence of rejection in the early months after transplantation have been reported in renal transplant patients with trough level MPA concentrations (measured by HPLC) of ≥ 1.3 μg/mL [4.1 μmol/L] with co-administration of cyclosporine and ≥ 1.9 μg/mL [5.9 μmol/L] with co-administration of tacrolimus.

An upper therapeutic limit based on development of toxicity has not been clearly established".

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.