

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

A. 510(k) Number:

k063520

B. Purpose for Submission:

New Device

C. Measurand:

Mycophenolic Acid (MPA)

D. Type of Test:

Quantitative

E. Applicant:

Roche Diagnostics Corp

F. Proprietary and Established Names:

Total Mycophenolic Acid

Total MPA Calibrators

Total MPA Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
OAV	II	21 CFR 862.3840	Clinical Toxicology
DLJ	II	21 CFR 862.3200	Clinical Toxicology
LAS	I	21 CFR 862.3280	Clinical Toxicology

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The COBAS INTEGRA Mycophenolic Acid cassette (MPA) contains an in vitro diagnostic reagent system intended for use of COBAS INTEGRA systems for the quantitative determination of total mycophenolic acid in human serum or plasma as an aid in the management of mycophenolic acid therapy in renal and cardiac transplant patients.

The Roche Total MPA Calibrators are designed for the calibration of the Roche Total MPA assay for the quantitative determination of mycophenolic acid in human serum and plasma on Roche automated clinical chemistry analyzers. The diluent is negative human serum and may be used for dilution of high samples or as a blank sample.

The Roche Total MPA controls are for use in quality controls by monitoring accuracy and precision for the quantitative methods as specified in the enclosed value sheet.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For the use on the COBAS INTEGRA systems

I. Device Description:

The Total MPA assay is a dual reagent assay. Reagent 1 is a mutant inosine monophosphate dehydrogenase II enzyme (IMPDH II) and IMP stabilizers and buffers. Reagent 2 is comprised of NAD, stabilizers and buffers.

The Total MPA calibrators are six levels of ready to use calibrators. The kit contains 6 vials of levels A to F (5 mL each) and one vial of diluent (10 mL). The diluent is negative human serum and may be used for dilution of high samples or as a blank sample. Levels A to F correspond to 0, 1, 3, 5, 10 and 15 µg/mL respectively. The product has been prepared exclusively from the blood of donors tested individually and shown by FDA-approved methods to be free from HBsAg and antibodies to HCV and HIV.

The Total MPA control set is a tri-level ready to use serum liquid based control set. The kit contains 2 vials of levels I to III (5 mL each). Levels I to III corresponds to approximately 0.86, 3.40 and 11.96 µg/mL, respectively. The product has been prepared exclusively from the blood of donors tested individually and shown by FDA-approved methods to be free from HBsAg and antibodies to HCV and HIV.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Microgenics CEDIA Sirolimus Assay

Microgenics CEDIA Sirolimus Calibrators Kit

Microgenics CEDIA Sirolimus Controls Kit

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

k034069

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Target Population	Renal and Cardiac Transplant Patients	Renal Transplant Patients

Differences		
Item	Device	Predicate
Intended use	Quantitative determination for total mycophenolic acid in human serum or plasma as an aid in the management of mycophenolic acid therapy in renal and cardiac transplant patients	Quantitative determination for sirolimus in human whole blood using automated clinical chemistry analyzers as an aid in the management of sirolimus therapy in renal transplant patients taking sirolimus.
Methodology	Enzyme-mimicking assay with MPA concentration inversely proportional to the formation of NADH.	Enzyme immunoassay with Sirolimus concentration directly proportional to a generated color change.

Differences		
Item	Device	Predicate
Reagent Format	Liquid	Lyophilized
Matrix	Nonhemolyzed human serum or EDTA Plasma (K ₂ or K ₃ EDTA)	Whole blood treated with EDTA
Range	0.4 – 15 ug/mL, extendable with post-dilution to 50 ug/mL.	5.0 – 30 ng/mL

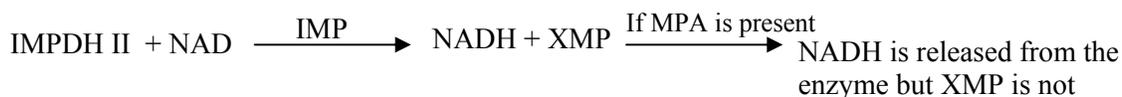
K. Standard/Guidance Document Referenced (if applicable):

None referenced by sponsor.

L. Test Principle:

The Roche Total MPA assay is a two-reagent system that utilizes a fixed amount of mutant IMPDH II (in reagent I). IMPDH II combines with a fixed amount of IMP and NAD to form NADH which is measured at 340 nm. The formation of NADH is inhibited when MPA is present in the serum or plasma samples. MPA concentration is inversely proportional to the rate of NADH formation. The reagents used to measure MPA concentration in serum or plasma are designed to mimic the *in vivo* mechanism of the enzyme.

In vivo mechanism



Roche Total MPA assay mimicking in vivo



M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Within-run precision was assayed using 21 replicates of three MPA controls and two human plasma pools. MPA-free patient plasma pools were prepared and spiked to low (sub-therapeutic) and high (therapeutic) levels with MPA. The results are summarized in the table below.

Material	TDM I	TDM II	TDM III	HSP 1	HSP 2
Mean (µg/mL)	0.84	3.43	12.12	1.46	9.08
SD (ug/mL)	0.01	0.02	0.11	0.01	0.05
CV %	1.4	0.5	0.9	0.8	0.5
N	21	21	21	21	21

Within-run, between-day and total imprecision were assessed for seven samples; 3 levels of controls and 4 human plasma pools. The samples were analyzed in triplicate, once a day for 21 days (n=63) on the COBAS Integra 700. Between-day results were obtained from the second replicate from the triplicate run. Two of the human plasma pools (HP1 and HP2) were MPA-free and spiked to low and high levels. The remaining two human plasma pools were prepared from samples taken from patients on MPA therapy (clinical low and high). Results are summarized below.

Specimen	MPA I	MPA II	MPA III	HP 1	HP 2	Clinical Low	Clinical High
Total Mean µg/mL	0.93	3.54	12.37	1.57	9.35	1.61	6.36
Within Run SD µg/mL	0.011	0.015	0.056	0.013	0.041	0.014	0.044
Within Run CV%	1.1%	0.4%	0.5%	0.9%	0.4%	0.8%	0.7%
Total SD µg/mL	0.042	0.065	0.163	0.038	0.141	0.035	0.113
Total CV%	4.5%	1.8%	1.3%	2.4%	1.5%	2.2%	1.8%
Between-day µg/mL SD	0.041	0.063	0.153	0.035	0.135	0.032	0.104
Between-day CV%	4.4%	1.8%	1.2%	2.2%	1.4%	2.0%	1.6%

The sponsor also conducted a CLSI precision study on the COBAS 400. Within-run, between-day and total imprecision was conducted on 3 levels of Roche total MPA controls and two human plasma pools. Each sample was assayed in triplicate daily for 10 days. Between day results were obtained from the second replicate from the triplicate run. The results are summarized in the table below.

Specimen	MPA I	MPA II	MPA III	HP I	HP II
Total Mean µg/mL	0.91	3.48	12.22	1.55	9.11
Within Run SD µg/mL	0.019	0.037	0.034	0.027	0.074
Within Run CV%	2.0%	1.1%	0.3%	1.7%	0.8%
Total SD µg/mL	0.041	0.061	0.090	0.047	0.081
Total CV%	4.5%	1.8%	0.7%	3.0%	0.9%
Between-day SD µg/mL	0.037	0.049	0.083	0.039	0.034
Between-day CV%	4.1%	1.4%	0.7%	2.5%	0.4%

The sponsors' two clinical sites also conducted within-run, between-day and total imprecision studies on 3 levels of Roche Total MPA controls, one level of MPA calibrator and 3 levels of human plasma pools. The material was assayed in triplicate measurement in 1 run per day on each of 21 days. Between-day results were calculated using the second replicate from each 3-fold determination. Plasma pools were prepared using samples from subjects who were not on MPA therapy. These pools were spiked to sub-therapeutic or low-end reportable range. The reports for the 2 sites are summarized in the tables below.

Site 1- Integra 400

Specimen	MPA Control I	MPA Control II	MPA Control III	Calibrator BI	HP 1	HP 2	HP 3
Total Mean $\mu\text{g/mL}$	0.873	3.443	12.011	1.039	0.781	2.471	9.924
Within Run SD $\mu\text{g/mL}$	0.023	0.045	0.161	0.028	0.021	0.027	0.229
Within Run CV%	2.6	1.3	1.3	2.7	2.7	1.1	2.3
Total SD $\mu\text{g/mL}$	0.024	0.051	0.209	0.033	0.026	0.041	0.229
Total CV%	2.8	1.5	1.7	3.1	3.4	1.6	2.3
Between-day SD $\mu\text{g/mL}$	0.009	0.024	0.133	0.016	0.015	0.030	0.0
Between-day CV%	1.1	0.7	1.1	1.5	1.9	1.2	0.0

Site 2- Integra 800

Specimen	MPA Control I	MPA Control II	MPA Control III	Calibrator BI	HP 1	HP 2	HP 3
Total Mean $\mu\text{g/mL}$	0.895	3.519	12.298	1.065	0.840	2.585	10.339
Within Run SD $\mu\text{g/mL}$	0.018	0.026	0.094	0.019	0.023	0.022	0.093
Within Run CV%	2.0	0.7	0.8	1.8	2.7	0.9	0.9
Total SD $\mu\text{g/mL}$	0.027	0.038	0.106	0.026	0.028	0.041	0.131
Total CV%	3.0	1.1	0.9	2.4	3.3	1.6	1.3
Between-day SD $\mu\text{g/mL}$	0.020	0.028	0.049	0.017	0.016	0.034	0.093
Between-day CV%	2.3	0.8	0.4	1.6	1.9	1.3	0.9

b. Linearity/assay reportable range:

The sponsor conducted six linearity recovery studies to validate the claimed measuring range of 0.4 to 15.0 $\mu\text{g/mL}$ for the Total MPA assay.

Full-range linearity (up to 15 $\mu\text{g/mL}$) was assessed for the following:

- non clinical spiked plasma pools (donors not on MPA therapy),
- clinical plasma pools from renal transplant patients taking MPA and spiked with additional MPA

- clinical plasma pools from cardiac transplant patients taking MPA and spiked with additional MPA.

The samples were spiked with MPA to >20% higher than the upper limit of the assay range (15 ug/mL) and combined with a 0 or low clinical plasma pool in varying portions to create systematic dilutions from low levels to >15 ug/mL.

Low-end linearity (0 to approximately 5 ug/mL) was assessed for the following:

- non clinical plasma pools (donors not on MPA therapy),
- clinical plasma pools from renal transplant patients taking MPA and spiked with additional MPA
- clinical plasma pools from cardiac transplant patients taking MPA and spiked with additional MPA.

The results of the linearity recovery studies in the form of recovery ranges (%) for the claimed assay range is shown in the table below.

	Measured Value (ug/mL)	Theoretical Value (ug/mL)	Recovery %
Study 1- Non-clinical plasma pools spiked with MPA (full-range)	15.73	17.00	92.53
	14.27	14.88	95.53
	12.70	12.75	99.61
	10.89	10.63	102.49
	8.90	8.5	104.71
	6.53	6.38	102.43
	4.25	4.25	100.00
	1.93	2.13	90.82
Study 2-clinical plasma pools from renal transplant patients taking MPA (full-range)	14.71	15.01	97.98
	12.67	12.67	100
	10.84	10.33	104.98
	8.19	7.98	102.61
	5.66	5.64	100.4
	2.99	3.29	90.77
	0.95	0.95	100
Study 3- Clinical plasma pools from cardiac transplant patients taking MPA (full-range)	14.81	15.07	98.27
	13.02	12.73	102.28
	10.8	10.4	103.95
	8.46	8.05	105.09
	5.7	5.71	99.82
	3.13	3.37	92.88
	1.03	1.03	100

	Measured Value (ug/mL)	Theoretical Value (ug/mL)	Recovery %
Study 4- Non-clinical plasma pools spiked with MPA (low-end)	5.12	4.91	104.1
	4.54	4.43	102.54
	3.94	3.94	100
	3.44	3.44	100
	2.9	2.95	98.25
	2.38	2.46	96.8
	1.88	1.97	95.6
	1.45	1.48	98.25
	1.02	0.98	103.7
	0.56	0.492	113.83*
Study 5- Clinical plasma pools from renal transplant patients taking MPA (low-end)	5.51	5.59	98.6
	4.57	4.69	97.35
	3.45	3.69	93.54
	2.31	2.57	89.86
	1.53	1.68	91.26
	0.96	1.01	95.44
	0.88	0.89	98.43
	0.68	0.671	101.4
	0.58	0.56	103.79
	0.5	0.45	111.84*
0.4	0.335	119.3*	
Study 6- Clinical plasma pools from cardiac transplant patients taking MPA (low-end)	5.63	6	93.83
	5.48	5.88	93.2
	4.47	4.92	90.85
	3.34	3.72	89.78**
	2.38	2.64	90.15
	1.52	1.68	90.48
	0.96	0.96	100
	0.87	0.84	103.57
	0.75	0.72	104.17
	0.67	0.6	111.67*
	0.56	0.48	116.67*
	0.48	0.36	133.33*
0.38	0.24	158.33*	

*Recovery exceeds 10% but is ≤ 0.3 ug/mL

** Recovery exceeds 10% and 0.3 ug/mL (by 0.08 ug/mL)

The sponsor conducted an extended measuring range study for the MPA assay. A manual dilution of samples with a post dilution factor of 5 is recommended in the product labeling. A 2000 ug/mL stock solution of MPA in methanol was spiked into normal human serum to produce serum samples with MPA concentrations of 15, 20, 25, 30, 33, 40, 50 and 55 ug/mL. Each sample was diluted 1:5 and 1:1 with the diluent from the

Total MPA calibrator kit (level A). Samples were measured in triplicate on both methods and the median results were compared. The 1:5 diluted samples had a recovery range of 97 to 105% and the 1:1 diluted samples has a recovery range of 92 to 108%. The results demonstrate acceptable recovery for dilution of samples with concentrations between 15 and 50 ug/mL with the diluent provided.

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

The Total MPA assay calibrators and controls are prepared gravimetrically to target levels and are verified against a validated HPLC method. The MPA used in the reagent, calibrators, and controls are traceable to an internally prepared mycophenolic acid. No USP material is available for MPA.

The Roche Total MPA Reagent was evaluated for closed shelf-life (accelerated and real-time) and open on-board stability for the MPO reagent. The results support a 15 month shelf life claim at 4 to 8° C for the MPO reagent. Real time stability studies are ongoing. The open on-board stability claim is 84 days.

Real time stability studies are ongoing for the Total MPA Controls (3 levels- 0.80, 3.5 and 12 µg/mL) Calibrators (2 levels- 5.0 and 15.0 µg/mL) and have been tested to date for 22 months. The accelerated study results support an 18 month closed stability claim. Open bottle stability support the open bottle package insert claims for calibrators and controls stability (6 months when stored at 2- 8 °C).

d. Detection limit:

The sponsor conducted a lower detection limit study with zero calibrator. The zero calibrator was assayed 21 times and the mean and SD of the 21 measured absorbance values was calculated. The mean mAbs value- 2SD of the replicates was calculated as 0.3 µg/mL.

The sponsor conducted a functional sensitivity study to determine the concentration at which acceptable assay precision is observed. The testing was performed using 8 samples from patients on MPA therapy with concentrations between 0.3 and 1.06 ug/mL. Samples were assayed in triplicate in one run per day for 10 days (n=30). Samples at 0.4 ug/mL showed 20% CV. The sponsor designated 0.4 g/mL as the low end of the assay's measuring range.

e. Analytical specificity:

The sponsor conducted specificity studies for the major MPA metabolites, mycophenolic acid glucuronide (MPAG), and the acyl glucuronide of MPA (AcMPAG). The metabolites were added to normal human plasma containing two concentrations of MPA (1.7 and 8.3 ug/mL). Samples and controls were run in triplicate. Samples containing a metabolite were run on the HPLC simultaneously in order to measure and subtract out the amount of MPA hydrolyzed from the metabolites. The percent cross reactivity equation is:

$$\frac{[\text{Control Recovery} - (\text{sample recovery} - \text{HPLC})]}{\text{Metabolite concentration}} * 100 \text{ or}$$

$$\frac{[\text{Column F} - (\text{Column D} - \text{Column E})]}{\text{Column C}} * 100$$

The concentrations and results are shown in the table below.

Column A	Column B	Column C	Column D	Column E	Column F	Column G
Compound	MPA Conc in Sample (ug/mL)	Cross Reactant Conc (ug/mL)	Observed MPA test Conc (ug/mL) in sample	HPLC MPA Conc (ug/mL)	MPA Control Conc (ug/mL)	% Cross Reactivity
MPAG	1.7	1000	2.63	1.03	1.56	0.004 %
MPAG	8	1000	8.96	1.03	7.76	0.017 %
AcMPAG	1.7	10	2.37	0.27	1.54	5.60 %
AcMPAG	8	10	8.39	0.27	7.64	4.80 %

Endogenous substances and co-administered drugs were tested in an interference study. Eight endogenous substances were tested to the highest concentration expected and one hundred and three co-administered drugs were tested to a 3-fold level higher than the highest concentration reported following therapeutic dosage. Samples were measured in triplicate with two levels of MPO (high and low) and the median was used to determine the deviation from the control sample. The following charts are a summary of the reported results.

	Interferent conc Range (mg/dL)	MPO analyte result range (ug/mL)	MPO recovery range (%)
Hemoglobin (µg/mL)			
[MPA] High- 8.53	1 -1108	8.60 – 8.24	100.2- 96.6
[MPA] Low- 1.322	0- 1226	1.35 – 1.29	102.3 – 98.5
Labeling states “No Significant interference up to 1000 mg/dL”.			
Conjugated Bilirubin (mg/dL)			
[MPA] High- 9.49	0 – 78	9.49 – 10.08	106.5- 102.0
[MPA] Low- 1.57	0 – 79	1.57 – 1.68	100.0 – 107.0

Unconjugated Bilirubin			
[MPA] High- 9.15	0 – 28	9.15 – 10.02	102.3- 109.5
[MPA] Low- 1.49	0 – 64	1.49 – 1.63	101.3 – 109.4
Labeling states “ No significant interference up to an I index of 66 for conjugated and 17 mg/dL for unconjugated bilirubin”.			
Lipemia (with intralipid)			
[MPA] High- 9.18	43 – 154	9.18 – 10.08	101.2 – 109.8
[MPA] Low 1.45	58 – 166	1.45- 1.58	100.0 – 109.0
Labeling states “No interference up to 93 mg/dL for intralipid” and the limitations states to “Avoid the use of lipemic specimens”.			
Clinical Triglycerides			
[MPA] High- 12.19	336- 926	12.19- 13.34	99.3- 109.4
[MPA] Low- 4.70	74- 885	4.70 – 5.01	97.9- 106.6
Labeling states “ No significant interference up to a triglycerides level of 500 mg/dL with a recovery specification of +/- 10 % or 600 mg/dL with a recovery specification of +/- 15%. No significant interference up to a intralipid level of 93 mg/dL. There is poor correlation between the L index (turbidity) and triglycerides concentration. Avoid the use of lipemic specimens”.			
Total Proteins			
[MPA] High- 9.45	2 – 11	9.14- 10.37	96.7 – 109.7
[MPA] Low- 2.23	4-11	2.12 – 2.37	95.1 – 106.3
Labeling states “ No significant interference from total protein concentrations of 4 -11 g/dL”.			
Albumin			
[MPA] High- 11.0	4.51-5.43	10.28- 11.23	91.5 (only one level)
[MPA] Low- 2.2	4.51-6.32	2.1-2.3	91.3-96.5
The sponsor states no significant interference up to 5.4 g/dL albumin.			
Gamma Globulin			
[MPA] High- 11.0	0 -9.92	9.24-10.25	90.1- 99.8
[MPA] Low- 2.2	0-6.20	1.96-2.16	90.7-98.6
The sponsor states no significant interference up to 6.2 g/dL Gamma Globulin.			
Cholesterol			
[MPA] High- 8.2	3- 503	8.2- 8.42	100.2 – 102.7
[MPA] Low- 1.79	3- 525.9	1.79- 1.83	100.0 – 102.8
Labeling states “No significant interference up to 500 mg/dL cholesterol”.			
Creatinine			
[MPA] High- 10.59	0.7 – 10.8	10.28 – 10.59	98.2 – 99.7
[MPA] Low – 1.93	0.7- 10.9	1.93 – 1.96	100.0 – 102.6
Labeling states “ No significant interference up to 10 mg/dL”.			
Uric Acid			
[MPA] High- 9.96	1.84- 21.18	9.92- 10.03	99.4- 100.7
[MPA] Low – 1.70	6.04 – 25.61	1.68 – 1.71	98.8 – 100.6
Labeling states “ No significant interference up to 20 mg/dL uric acid”.			

Additionally, the sponsor evaluated the effects of 103 potential drug interferences on the MPA assay on two levels of MPA (approximately 1.5 and 9.0 µg/mL). The samples were measured in triplicate and the median was used to determine the deviation from the control sample. The possible drug interferents were tested at 3X the normal plasma concentrations and there were no significant interferences were caused by the drugs (except for intralipid interference) listed in the package insert.

The sponsor conducted additional studies to establish time, temperature and freeze/thaw cycles for the MPA samples used with the Total MPA Assay. Samples were aliquotted and stored at 15-25° C, 2-8° C and -20° C. Frozen samples were thawed on the day tested. Samples were measured in triplicate in several time intervals over the course of at least four weeks. The sponsor states that results for plasma sample are stable for 3 months at -20° C and 2-8° C, and for 4 weeks at 25° C. The sponsor's serum results support stability for 4 weeks at -20° C, 2-8° C and 25° C and 5 freeze thaw cycles for serum samples.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The sponsor conducted a three part, four site clinical study to compare the performance characteristics of the Roche Total Mycophenolic Acid assay on the Integra platform to HPLC MPA measurements. Inclusion/ exclusion criteria are described below.

Inclusion criteria:

Patient:

Renal or cardiac transplant recipient who is taking MPA as an immunosuppressant and who consents to participate in the study, where consent required by law.

Persons for whom less than 2 samples have already been used in this trial.

Sample:

Serum collected without a gel separation tube or EDTA K₃ or K₂ plasma in sufficient volume to complete the required method comparison analysis.

Exclusion Criteria

Patient:

All other transplant types besides renal and cardiac

Transplant recipients who are not taking MPA

Any non-transplant patient who is taking MPA

Persons not consenting to the trial, where consent is required by law.

Persons for whom 2 samples have already been used in this trial

Site 1: US

Site 2: Germany

Site 3: France

Site 4: Roche Diagnostics

The first part of the study tested EDTA plasma specimens from renal and cardiac (148 and 117 samples from 209 patients respectively) transplant recipients (n=265) at site 1 whose immunosuppressant drug regime includes mycophenolate mofetil or mycophenolate sodium (MPA). Samples were assayed fresh at the immunochemistry labs then stored frozen at -20 °C. The residual plasma samples were tested in parallel on the HPLC and Integra 400 Plus.

The second part of the study tested banked residual renal EDTA plasma samples (147 samples from 86 patients) from a Roche Pharmaceutical MPA study that was performed at approx. 70 sites in Europe and included renal samples from patients in France (that were stored in Germany). All samples were from patients whose immunosuppressant drug regimen includes mycophenolate mofetil or mycophenolate sodium (MPA). The parallel testing was performed on HPLC and Integra 800 at site 2.

The third part of the study tested 159 residual EDTA plasma specimens from renal (89) and cardiac (70) transplant recipients from Site 1 whose immunosuppressant drug regimen included mycophenolate mofetil or mycophenolate sodium (MPA). The samples obtained from Site 1 were tested on the Integra 700 and were different from the samples that were tested at site 1. All patients had received either renal or cardiac allografts and were on bid (twice daily) MPA therapy.

The sponsor calculated regression slopes, intercepts, and correlation coefficients according to Passing/Bablok methods. The method comparison results for all three sites are shown in the chart below.

(Site 1) Integra 400							
Methodology vs HPLC	Slope (95% CI) µg/mL	Intercept (95% CI) µg/mL	Correlation Coefficient	Sample Size	Sample Range µg/mL	Neat Sample Range µg/mL	Spiked Sample Range µg/mL
Renal	1.010 (0.988-1.035)	0.068 (0.034-0.105)	0.995	148	0.40-14.80	0.40 – 13.70	7.9-14.80

Cardiac	1.014 (0.996- 1.031)	0.057 (- 0.004- 0.103)	0.992	114	0.40- 13.60	0.40- 11.20	6.40- 13.60
Combined	1.011 (1.000- 1.025)	0.064 (0.038- 0.090)	0.993	265	0.40- 14.80		
Site 2- Integra 800							
Renal	1.100 (1.073- 1.120)	-0.1200 (-.1920- 0.0656)	0.994	147	0.50- 14.70	0.500 – 14.70	None
Site 3 – Integra 700							
Renal	1.062 (1.044 – 1.079)	0.019 (-0.021- 0.073)	0.997	89	0.46- 13.57	0.460- 9.077	5.34- 13.57
Cardiac	1.088 (1.050- 1.125)	-0.023 (-0.110- 0.045)	0.993	70	0.57- 14.22	0.573- 9.914	5.96- 14.22
Combined	1.068 (1.052- 1.085)	0.005 (-0.003- 0.050)	0.995	159	0.46- 14.22		

The sponsor also conducted imprecision testing at the external sites, as discussed in the precision section above.

b. Matrix comparison:

A serum/plasma comparison study was conducted for all sample types that the sponsor recommends for use with the MPA total assay. The serum/EDTA plasma paired samples from 50 donors were spiked and tested in triplicate with the MPA assay on the Integra 700. The samples were compared in the following combinations:

Serum vs. EDTA,

K₃ EDTA vs. K₂ EDTA,

K₃ EDTA vs. K₂ EDTA (half filled tubes) and

K₃ EDTA vs. K₃ EDTA (half filled tubes)

Each sample was measured in triplicate. The median was calculated and serum and plasma results were compared by a method comparison. The slope, intercept, and correlation coefficient (Passing/Bablok) were determined. The results for each comparison are shown in the chart below.

Comparison	Method	N	Range	Slope	Intercept	R
1	X: K3 EDTA	50	1.230-15.310	0.988	-0.003	0.9977
	Y: Serum					
2	X: K3 EDTA	50	1.230-15.310	0.992	-0.054	0.9984
	Y: K2 EDTA					
3	X: K3 EDTA	11	1.750- 13.550	0.951	0.195	0.9977
	Y: K2 EDTA (half)					
4	X: K3 EDTA	8	1.230- 14.300	1.016	0.018	0.9992
	Y: K3 EDTA (half)					

K₂ EDTA, K₃ EDTA, and serum samples all met the sponsors predetermined acceptance criteria.

3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable – This information is not typically provided for immunosuppressant TDM assays.

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 cites multiple studies from the literature concerning the expected values (therapeutic range) in the package insert and articles to support their claim expected values. The package insert states:

“The therapeutic range of mycophenolic acid is not fully established and is dependent on transplant type and coadministered drugs. Optimal mycophenolic acid assay values to prevent rejection may vary based on the test system and therefore should be established for each test system”.

“Decreased incidences of rejection in the early months post-transplantation have been reported in renal transplant patients with predose MPA concentrations (measured by HPLC) of $\geq 1.3 \mu\text{g/mL}$ with coadministration of cyclosporine and $\geq 1.9 \mu\text{g/mL}$ with coadministration of tacrolimus.^{1,2} An upper therapeutic range based on development of toxicity has not been established. The clinical ramifications of MPA concentrations beyond the early post transplantation period are not yet known.¹

Cardiac transplant patients, predose MPA concentrations (measured by HPLC) of 1.2 – 3.5 $\mu\text{g/mL}$ have been recommended to minimize incidences of rejection.^{1,3} Higher predose concentrations ($\geq 2.5 \mu\text{g/mL}$) in the early post-transplantation period (<6 months) have also been suggested.^{3,4,5} Pediatric cardiac transplant patients have been shown to require higher doses of MPA in comparison to adults due to differences in MPA metabolism.^{1,3,4,6}

1) 3. Van Gelder T, Meur YL, Shaw LM, Oellerich M, DeNofrio D, Holt C, Holt DW, Kaplan B, Kuypers D, Meiser B, Toenshoff B, Mamelock RD. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006; 28(2): 145-154.

2) Cox VC, Ensom MHH. Mycophenolate mofetil for solid organ transplantation: Does the evidence support the need for clinical pharmacokinetic monitoring? *Ther Drug Monit*(3) 2003; 25(2): 137-157.

3) Meiser BM. Therapeutic drug monitoring of mycophenolic acid in cardiac transplant recipients: does it make sense? *Curr Opin Organ Transplant* 2005; 10: 350-354.

4) Gajarski RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? *Am J Transplant* 2004; 4:1495-1500.

5) Meiser BM, Reichart B. New agents and new strategies in immunosuppression after heart transplantation. *Curr Opin Organ Transplant* 2002; 7: 226-232.

6) Dipchand AI, Pietra B, McCrindle BW, Rosebrook-Bicknell HL, Boucek MM. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. *J Heart Lung Transplant*. 2001; 20(10): 1035-1043.

The sponsor notifies users to investigate the transferability of the expected values to its own patient population and if necessary determine its own reference range. For diagnostic purposes the test findings should always be assessed in conjunction with the patient’s medical history, clinical examinations, and other findings.

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.