

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

A. 510(k) Number:

k150168

B. Purpose for Submission:

New Device

C. Measurand:

Tacrolimus

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Tacrolimus Flex® Reagent Cartridge (TAC)

Dimension Tacrolimus Calibrator (TAC CAL)

G. Regulatory Information:

1. Regulation section:

21 CFR §862.1678, Tacrolimus Test System

21 CFR §862.1150, Calibrator

2. Classification:

Class II

3. Product code:

MLM, JIT

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Dimension Tacrolimus Flex® Reagent Cartridge (TAC) is an in vitro diagnostic test for the quantitative measurement of tacrolimus in human whole blood on the Dimension® clinical chemistry system. Measurements of tacrolimus are used as an aid in the management of tacrolimus therapy in renal and hepatic transplant patients.

The Dimension Tacrolimus Calibrator (TAC CAL) is an in vitro diagnostic product for the calibration of the Tacrolimus (TAC) method on the Dimension® clinical chemistry system.

3. Special conditions for use statement(s):

Prescription use only

The instrument reporting system contains flags and comments to provide the user with information regarding instrument processing errors, instrument status information and potential errors in TAC results. Refer to the Dimension® Operator's Guide for the meaning of report flags and comments. Any result containing flags and/or comments should be addressed according to your laboratory's procedure manual.

Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. Antibodies to β -galactosidase can be encountered in samples as a consequence of bacterial infection and may produce falsely elevated results which may not be consistent with clinical evaluation. The assay has been designed to minimize interference from antibodies to β -galactosidase. In very rare instances, immunoassays may produce falsely elevated or decreased results due to other patient-specific interferents. A number of these interferents are present in the plasma of affected patient samples and will be detected by the automatic rerun procedure. Complete elimination of such interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution. Confirmation of unexpected or atypical results by an alternative methodology is recommended prior to any adjustments in tacrolimus dosage. For patients with impaired liver function and patients receiving other drugs which may induce or inhibit microsomal enzyme activity, the routine use of the Dimension® Tacrolimus assay may be supported by HPLC data to assess possible changes in biotransformation and elimination.

If TACR (Cat.No. DF107) and TAC (Cat. No. DF207) assays are processed on the same instrument, there is a remote potential for carryover from the TACR pretreatment reagent to produce falsely elevated results with the TAC assay. This potential has been mitigated as much as possible through the instrument software.

If use of the TAC and TACR assays on the same instrument cannot be avoided, as a further safeguard, each run of the TAC assay should be immediately preceded by flushing the reagent and sample probes (10 cycles) using the Prime Pump routine (SYSTEM PREP, PUMP PRIME, PRIME WATER). TAC reagent hydrations should also be preceded by flushing of the probes using this routine. Laboratories should convert as rapidly as possible to consistent use of the TAC assay for individual patients, discontinue use of the TACR assay and remove any remaining TACR reagent from the instrument inventory.

4. Special instrument requirements:

The Dimension® clinical chemistry system

I. Device Description:

The automated Dimension® TAC method is performed using a method specific Flex® reagent cartridge. The reagents for this assay are packaged in an 8-well Flex® Reagent Cartridge that contains a pretreatment reagents, antibody-β-galactosidase conjugate, tacrolimus immobilized on chromium dioxide particles, chlorophenol red β-d-galactopyranoside (CPRG) substrate, and diluent to hydrate the tablets.

Dimension® Tacrolimus (TAC) Calibrator is five level frozen liquid, whole blood hemolysate containing purified tacrolimus. The product is provided in 4.0 mL vials, 2 vials per level. There are five calibrator levels per kit which span the assay range for the Dimension® Tacrolimus (TAC) assay. The calibrators are packaged at 1.0 mL per vial for levels 2 – 5. Level 1, calibrator base with no tacrolimus has 2.0 mL per vial so that it can also be used as a high sample diluent.

Each level of TAC Calibrator is prepared from human whole blood hemolysate base. Levels 2 – 5 are spiked with purified tacrolimus drug to achieve target concentrations of 3 ± 1 ng/mL; 6 ± 1 ng/mL; 12 ± 2 ng/mL and >30.0 ng/mL. Level 1 calibrator has no drug added.

The calibrator package insert contains the following caution: “Contains human source material. Each donor unit used in the preparation of this product was tested by FDA-approved methods for the presence of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2), as well as for Hepatitis B surface Antigen and antibody to Hepatitis C Virus (HCV), and found to be negative (not repeatedly reactive). Because no testing can offer complete assurance that these or other infectious agents are absent, this material should be handled using good laboratory practice to avoid skin contact and ingestion”.

J. Substantial Equivalence Information:

1. Predicate device name(s):

ARCHITECT Tacrolimus Assay

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

k070820

3. Comparison with predicate:

Item	Device Dimension® TAC Flex® reagent cartridge	Predicate ARCHITECT Tacrolimus Assay (k070820)
Similarities		
Intended Use	For the quantitative measurement of tacrolimus in human whole blood as an aid in the management of tacrolimus therapy in renal and hepatic transplant patients	Same
Assay type	Immunoassay	Same
Sample Type	Whole blood in EDTA	Same
High Sample Dilution	Manual	Same
Differences		
Instrument	The Dimension® clinical chemistry system	The Abbott ARCHITECT i System
Sample Pretreatment	No manual pretreatment	Manual pre-treatment
Measuring Range	1.0 – 30 ng/mL	2 – 30 ng/mL
Cross reactivity Profile M-I	1%	8%
M-II	18%	94%
M-III	15%	45%
M-IV	99%	9%
M-V	1%	Not Available
M-VI	1%	Not Available
M-VII	43%	Not Available
M-VIII	0%	Not Available

Item	Device TAC CAL	Predicate TACR CAL (k060503)
Similarities		
Intended Use	For the calibration of the Tacrolimus (TAC) method on the Dimension® clinical chemistry system.	Same
Form	Frozen Liquid	Same

Matrix	Whole blood hemolysate	Same
Levels	Five	Same
Traceability	Purified tacrolimus	Same
Differences		
Assignment	Assigned for Dimension® TAC	Assigned for Dimension® TACR
Target Concentration Range	Level 1: - 0.5 to + 0.5 ng/mL Level 2: 2.7 to 4.2 ng/mL Level 3: 5.8 to 7.3 ng/mL Level 4: 11.6 to 13.6 ng/mL Level 5: ≥30.0 ng/mL	Level A: - 0.7 to + 0.7 ng/mL Level 2: 2.5 to 4.0 ng/mL Level 3: 5.5 to 7.0 ng/mL Level 4: 11.0 to 13.0 ng/mL Level 5: 31.0 to 34.0 ng/mL

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

- CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods
- CLSI EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
- CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition
- CLSI EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline
- FDA Guidance document “Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA” – 09/16/2002.

L. Test Principle:

The Dimension® TAC method is an automated immunoassay in which free and tacrolimus-bound antibody-enzyme conjugate is separated using magnetic particles. The tacrolimus present in the sample is bound by the tacrolimus antibody. Magnetic particles coated with tacrolimus are added to bind free (unbound) antibody-enzyme conjugate. The reaction mixture is then separated magnetically. Following separation, the supernatant containing the tacrolimus-antibody-enzyme complex is transferred to a cuvette and mixed with the substrate; chlorophenol red β-d-galactopyranoside (CPRG). β-galactosidase catalyzes the hydrolysis of CPRG to produce chlorophenol red (CPR) that absorbs light maximally at 577 nm. The change in absorbance at 577 nm due to the formation of CPR is directly proportional to the amount of tacrolimus in the patient’s sample and is measured using a bichromatic (577, 700 nm) rate technique.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision of the Dimension® TAC method was evaluated at two external testing sites, and at Siemens internal laboratory following EP5-A. Whole blood patient pools and control materials were chosen at concentrations which represented the sub-therapeutic, therapeutic and toxic range of the assay. For each test level, a single test from two independent cups was analyzed twice per day for 20 days (N=80). A single lot of reagent and calibrators was tested at each of the two external sites; whereas two additional lots of reagents were tested at the internal site to evaluate lot-to-lot variability. A whole blood sample with extremely low concentration of Tacrolimus was also tested at the internal site. The results are summarized below:

Internal site

Material	Mean ng/mL	Repeatability (N=4)		Total Precision (N=80)	
		SD	%CV	SD	%CV
Whole Blood Pool #1	1.8	0.11	6.1	0.22	12.1

Sample	Lot	Mean ng/mL	Repeatability (N=4)		Total Precision (N=80)	
			SD	%CV	SD	%CV
Whole Blood Pool #2	Lot 1	5.9	0.19	3.2	0.23	3.8
	Lot 2	5.8	0.16	2.7	0.18	3.1
	Lot 3	6.0	0.18	3.1	0.26	4.4
Whole Blood Pool #3	Lot 1	12.9	0.41	3.2	0.54	4.2
	Lot 2	13.5	0.37	2.7	0.49	3.6
	Lot 3	14.0	0.42	3.0	0.57	4.0
Whole Blood Pool #4	Lot 1	20.2	0.65	3.2	0.84	4.2
	Lot 2	21.6	0.59	2.7	0.89	4.1
	Lot 3	21.9	0.68	3.1	0.86	3.9
QC Level 1	Lot 1	5.1	0.16	3.1	0.23	4.6
	Lot 2	5.1	0.09	1.8	0.18	3.5
	Lot 3	5.2	0.18	3.5	0.20	3.9
QC Level 2	Lot 1	11.7	0.29	2.5	0.42	3.6
	Lot 2	12.2	0.33	2.7	0.48	3.9
	Lot 3	12.6	0.51	4.0	0.66	5.2

QC Level 3	Lot 1	28.3	1.12	3.9	1.40	4.9
	Lot 2	29.8	0.90	3.0	1.07	3.6
	Lot 3	29.5	0.83	2.8	1.22	4.1

External site 1

Material	Mean ng/mL	Repeatability (N=4)		Total Precision (N=80)	
		SD	%CV	SD	%CV
Whole blood Pool 1	1.8	0.16	8.3	0.26	14.0
Whole blood Pool 2	5.4	0.16	2.9	0.34	6.3
Whole blood Pool 3	13.1	0.29	2.2	0.61	4.6
Whole blood Pool 4	20.7	0.48	2.3	1.02	4.9
QC level 1	4.4	0.17	3.8	0.30	6.9
QC level 2	11.4	0.26	2.3	0.51	4.5
QC level 3	27.4	0.86	3.2	1.40	5.1

External site 2

Material	Mean ng/mL	Repeatability (N=4)		Total Precision (N=80)	
		SD	%CV	SD	%CV
Whole Blood Pool 1	1.8	0.12	6.6	0.24	13.1
Whole Blood Pool 2	5.1	0.18	3.6	0.31	6.0
Whole Blood Pool 3	13.0	0.28	2.2	0.52	4.0
Whole Blood Pool 4	20.8	0.49	2.4	0.96	4.6
QC level 1	4.3	0.14	3.3	0.23	5.3
QC level 2	11.6	0.30	2.6	0.49	4.2
QC level 3	28.7	0.88	3.1	1.63	5.7

b. *Linearity/assay reportable range:*

Linearity

A high tacrolimus native patient pool (40.6 ng/mL) and a patient pool with no tacrolimus were combined in different ratios to produce nine levels of patient pools which bracketed both the high and low end of the proposed assay range. The expected concentrations of the samples based on the dilution factors are 0.0, 5.1, 10.2, 15.2, 20.3, 25.4, 30.5, 35.6, 40.6 ng/mL. All nine pools were assayed in replicate of 4 on a single Dimension® analyzer. The measured values (Y) were compared to the expected values (X). The result of linear regression based on each replicate is summarized in the below table. The results below support the proposed measuring range of 1.0 – 30.0 ng/mL.

	Rep 1	Rep 2	Rep 3	Rep 4
Slope	1.021	1.011	1.016	1.025
Intercept	-0.12	+0.21	+0.16	+0.12
Correlation Coefficient	0.999	0.995	0.996	0.997

Spiked recovery

Recovery of tacrolimus by the Dimension TAC assay was determined by adding a known amount of USP standard tacrolimus to five human blood pools from patients receiving tacrolimus therapy. The results for the samples spiked with tacrolimus were compared to the control samples and the recovery was calculated using mean of 10 replicates of each sample. The sponsor defined acceptance criterion is 90-110% recovery of the expected value.

The results are summarized in the table below.

Dimension TAC - Spiked Recovery

Tacrolimus spiked amount (ng/mL)	Avg % Recovery	Range of % Recovery
4.2	96%	93-98%
7.2	95%	92-99%
8.3	94%	90-96%
10.7	103%	97-111%
11.6	98%	92-103%
12.3	99%	93-109%
14.7	98%	93-103%
16.7	101%	98-104%
13.9	103%	99-108%
18.3	102%	99-106%

Dilution recovery

Testing was performed to validate the manual dilution protocol (1:1 dilution on samples with results > 30.0 ng/mL) recommended by the manufacturer in the package insert. Four native serum samples, with tacrolimus concentrations >30 ng/mL on the Dimension® TAC assay, were used for this study. The expected values for these samples were assigned by LC-MS and ranged from 38.8 to 51.4 ng/mL. Two preparations of a 1:1 dilution of each sample were prepared using TAC Calibrator Level 1 as the diluent. Each aliquot of each sample tested in duplicate using the Dimension TAC method. The % recovery values after dilution are summarized below.

Dimension TAC – Dilution Recovery

Sample #	Expected Value	Observed Value Corrected for Dilution		Grand Mean	% Recovery
	ng/mL	ng/mL			
1	42.3	44.8	43.5	45.3	107.1
1	42.3	46.6	46.2		
2	38.8	41.8	41.4	41.7	107.5
2	38.8	42.3	41.3		

3	48.2	49.0	47.7	49.4	102.4
3	48.2	50.3	50.5		
4	51.4	57.2	54.0	56.4	109.8
4	51.4	56.8	57.7		
				Average	106.7

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

Traceability and expected values

Siemens Tacrolimus (TAC) Calibrators are traceable to an internal reference standard gravimetrically prepared and confirmed via HPLC. Calibrators' values must be within $\pm 1\%$ of the reference calibrator value.

Calibrator Stability

Real-time testing was performed. Protocols and acceptance criteria were reviewed and deemed acceptable. The shelf life for the Dimension TAC Calibrator is 12 months, at a storage temperature range of -15 to -25° C. Once thawed, assigned values are stable for 30 days when recapped immediately after use and stored at 2-8°C.

Sample Stability

The sponsor presented a study that supports the claim that whole blood samples collected in EDTA may be stored at 2 – 8 °C or at ambient room temperature (23.6°C to 24°C) for up to 8 days before testing. A freeze-thaw study was also conducted to validate that EDTA whole blood samples could be stored frozen (-20°C) and thawed prior to analysis without affecting test results.

d. *Detection limit:*

Analytical sensitivities were determined following EP17-A2. LoB and LoD were determined using 5 patient samples free of tacrolimus, and 5 patient samples with low tacrolimus levels ranging from 0.2 to 1.7 ng/mL. For limit of quantitation (LoQ), patient samples spiked with tacrolimus at 0.80, 0.85, 0.90, 0.95 and 1.00 ng/mL were tested. All samples were measured in replicates of 4 using two reagent lots over a period of 3 days. LoQ is defined as the lowest analyte concentration where the %CV at the upper 95% confidence limits is $\leq 20\%$.

The results are summarized in the below table.

	LoB (ng/mL)	LoD (ng/mL)	LoQ (ng/mL)
Lot 1	0.5	0.7	0.9
Lot 2	0.2	0.3	0.7
Claimed	0.5	0.7	1.0

e. *Analytical specificity:*

Interference testing was performed following EP-7A2. The compounds tested included endogenous compounds, drugs that are commonly co-administered with tacrolimus, as well as common over-the-counter drugs and the anticoagulant EDTA. The samples used for this study were prepared from whole blood to which purified tacrolimus drug was added to achieve target concentrations of 5ng/mL and 20ng/mL. Comparison between the test and control was done using the mean of five (5) replicates for each sample. The % difference between the spiked sample and the control sample with no substance was calculated. The sponsor defines no significant interference as bias within $\pm 10\%$. For compounds that showed $>10\%$ bias, a dose response study was performed to determine the highest concentration at which no interference is observed. No interference was observed with the exogenous compounds tested and a complete list of the compounds and results are tabulated in the package insert. The endogenous substances tested and the maximum allowed concentration with no interference are summarized in the below table.

Compound	Test Conc	%Recovery@ 5ng/mL TAC	% Recovery @ 20ng/mL TAC
Albumin	6 g/dL	101	100
Albumin	12 g/dL	96	92
Cholesterol Conjugated	500 mg/dL	91	99
Bilirubin Unconjugated	60 mg/dL	99	96
Bilirubin	60 mg/dL	96	95
Creatinine	30 mg/dL	103	103
IgG	6 g/dL	103	99
IgG	12 g/dL	95	99
Lipemia (Intralipid)	1000 mg/dL	92	94
Rheumatoid Factor	500 IU/mL	98	98
Total Protein	3-4 g/L	109	106
Total Protein	12 g/L	95	98
Triglycerides	1000 mg/dL	91	90
Urea	500 mg/dL	100	97
Uric Acid	20 mg/dL	101	96
Hematocrit	23.3 %	104	99
Hematocrit	49.8 %	102	100
HAMA	Positive Sample 1	104	109
HAMA	Positive Sample 2	105	105

Cross-reactivity:

Cross-reactivity was performed following EP-7A2. The samples used for this study were prepared from whole blood with or without the metabolite. Each sample was tested in replicate of 5 and the mean was used to calculate cross-reactivity using the below formula:

$$\% \text{ Cross-reactivity} = 100 \times (\text{Test-Control}) / \text{Concentration of Compound}$$

The results are summarized in the table below.

Cross-reactivity of Tacrolimus Metabolites

Metabolite	Concentration tested (ng/mL)	Concentration Detected (ng/mL)	%Cross Reactivity
Major Metabolite			
M I (13-O-desmethyl-tacrolimus)	40	0.2	1
Minor Metabolites			
M II (31-O-desmethyl-tacrolimus)	40	7.3	18
M III (15-O-desmethyl-tacrolimus)	40	6.0	15
M IV (12-O-hydroxyl-tacrolimus)	20	19.8	99
Second Pass Metabolites			
M V (15,31-O-didesmethyl-	40	0.3	1
M VI (13,31-O-didesmethyl-	40	0.2	1
M VII (13,15-O-didesmethyl-	40	17	43
M VIII (unknown name)	40	0	0
<u>Control</u>	0.0	0.5	

In the labeling, the sponsor has the following statement:

Patients undergoing retinal fluorescein angiography can retain amounts of fluorescein in the body for up to 36 to 48 hours post-treatment. In the cases of patients with renal insufficiency, including many diabetics, retention could be much longer. Such samples can produce falsely elevated values when tested with this assay, and should not be tested.

Triglycerides at 1500 mg/dL [16.9 mmol/L] decreases TAC results by -18.7 % at a TAC concentration of 5 ng/mL [6.5 nmol/L] and decreases TAC results by -12.1 % at 20 ng/mL [26.0 nmol/L].

Intralipid at 1500 mg/dL [16.9 mmol/L] decreases TAC results by -13.6 % at a TAC concentration of 5 ng/mL [6.5 nmol/L] and decreases TAC results by -18.6 % at a

TAC concentration of 20 ng/mL [26.0 nmol/L].

Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. Antibodies to β -galactosidase can be encountered in samples as a consequence of bacterial infection and may produce falsely elevated results which may not be consistent with clinical evaluation. The assay has been designed to minimize interference from antibodies to β -galactosidase. In very rare instances, immunoassays may produce falsely elevated or decreased results due to other patient-specific interferents. A number of these interferents are present in the plasma of affected patient samples and will be detected by the automatic rerun procedure.

Complete elimination of such interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.

Confirmation of unexpected or atypical results by an alternative methodology is recommended prior to any adjustments in tacrolimus dosage. For patients with impaired liver function and patients receiving other drugs which may induce or inhibit microsomal enzyme activity, the routine use of the Dimension® Tacrolimus assay may be supported by HPLC data to assess possible changes in biotransformation and elimination.

f. Assay cut-off:

Not applicable – this is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed at two external sites and an internal site using 3 lots of reagents (one lot/site). The collection protocol is the same across the 3 different sites, with approximately 100 patients enrolled at each site, and half from liver and half from kidney transplant patients. Each sample was tested in singlet using the candidate assay, and compared to the result of the predicate assay and the LC-MS method, respectively. The LC-MS method measures the parent drug of tacrolimus (MRM, mass transition of 821.6 m/z to 768.7 m/z). The exact number of patients tested at each site, and the Passing- Bablok regression analysis results are summarized in the below tables. The samples tested ranged from 1.2 – 25.6 ng/mL, which covered >80% of the assay range (1.0 – 30 ng/mL).

Site 1/Lot 1

Proposed TAC Assay versus	n	Slope	Intercept	Mean Bias	Std Dev.	R²
LCMS						
Total	102	1.00	-0.30	-0.22	1.01	0.977
Kidney only	50	1.05	-0.58	0.01	0.98	0.985
Liver only	52	0.90	0.14	-0.44	0.99	0.947
Abbott ARCHITECT						
Total	102	1.00	-0.40	-0.37	0.82	0.984
Kidney only	50	1.02	-0.55	-0.32	1.00	0.984
Liver only	52	1.00	-0.40	-0.43	0.61	0.975

Site 2/Lot 2

Proposed TAC Assay versus	n	Slope	Intercept	Mean Bias	Std Dev.	R²
LCMS						
Total	99	1.08	-0.31	0.19	0.67	0.986
Kidney only	49	1.08	-0.25	0.24	0.79	0.981
Liver only	50	1.07	-0.36	0.14	0.53	0.990
Abbott ARCHITECT						
Total	96	1.11	-0.93	-0.22	0.69	0.984
Kidney only	48	1.08	-0.82	-0.13	0.84	0.978
Liver only	48	1.11	-0.95	-0.32	0.50	0.993

Site3/lot3

Proposed TAC Assay versus	n	Slope	Intercept	Mean Bias	Std Dev.	R²
LCMS						
Total	114	1.05	-0.41	-0.33	1.32	0.945
Kidney only	59	1.13	-1.34	-0.68	1.53	0.922
Liver only	55	1.09	-0.33	0.05	0.91	0.974
Abbott ARCHITECT						
Total	110	0.90	-0.05	-0.85	0.90	0.983
Kidney only	56	0.95	-0.44	-0.86	0.77	0.982
Liver only	54	0.85	0.21	-0.84	1.02	0.988

b. Matrix comparison:

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

3. Clinical studies:

a. *Clinical Sensitivity:*

NA

b. *Clinical specificity:*

NA

c. Other clinical supportive data (when a. and b. are not applicable):

NA

4. Clinical cut-off:

Not applicable; this is a quantitative assay.

5. Expected values/Reference range:

The following is stated in the package insert:

No firm therapeutic range exists for tacrolimus in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of tacrolimus, co-administration of other immunosuppressants, type of transplant, time post-transplant, and a number of other factors will cause different requirements for optimal blood levels of tacrolimus. Individual tacrolimus values cannot be used as the sole indicator for making changes in the treatment regimen. Each patient should be thoroughly evaluated clinically before treatment adjustments are made. Each assay user must establish therapeutic ranges based on clinical experience. Therapeutic ranges vary according to the commercial test method used, and therefore should be established for each commercial test. Values obtained with different assay methods cannot be used interchangeably due to differences in assay methods and cross-reactivity with metabolites, nor should correction factors be applied. Therefore, consistent use of one assay for individual patients is 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.