

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

A. 510(k) Number:

k052017

B. Purpose for Submission:

New device

C. Measurand:

Cyclosporine

D. Type of Test:

Affinity Particle Mediated Immunoassay

E. Applicant:

DADE BEHRING, INC.

F. Proprietary and Established Names:

Dimension® Cyclosporine Extended Range Assay (CSAE) Flex® reagent cartridge

G. Regulatory Information:

1. Regulation section:
21 CFR §862.1235, cyclosporine test system
2. Classification:
Class II
3. Product code:
MKW, cyclosporine
4. Panel:
Toxicology (91)

H. Intended Use:

1. Intended use(s):
The Cyclosporine CSAE Flex® reagent cartridge is an in vitro diagnostic test intended to quantitatively measure cyclosporine A (CSA) in human whole blood for the Dimension® clinical chemistry system. Measurements of CSA are used as an aid in the management of heart, liver and kidney transplant patients.
2. Indication(s) for use:
The Cyclosporine CSAE Flex® reagent cartridge is an in vitro diagnostic test intended to quantitatively measure cyclosporine A (CSA) in human whole blood for the Dimension® clinical chemistry system. Measurements of CSA are used as

an aid in the management of heart, liver and kidney transplant patients.

3. Special conditions for use statement(s):

For professional use only

4. Special instrument requirements:

The Cyclosporine Extended Range Assay (CSAE) assay requires one of the following instruments:

- Dade Behring Dimension® RxL clinical chemistry system (K944093)
- Dade Behring Dimension® RxL Max clinical chemistry system (K 944093)
- Dade Behring Dimension® Xpand clinical chemistry system (K010061)
- Dade Behring Dimension® Xpand PLUS clinical chemistry system (K010061)

I. Device Description:

The Dimension® CSAE Cyclosporine Flex® reagent cartridge (DF108) is an in vitro diagnostic device that consists of prepackaged reagents in a plastic eight well cartridge for use on the Dade Behring Dimension® clinical chemistry system. Reagent contents are described in the ‘Test Principle’ section below.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Abbott TDx/TDx FLx ® Cyclosporine Assay

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

k040761

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Indications for use	Measurements of CSA to be used as an aid in the management of heart, liver and kidney transplant patients	same
Matrix	Whole blood	same
Detection Antibody	mouse monoclonal	same

Differences		
Item	Device	Predicate
Detection Technology	Affinity Particle Mediated Immunoassay	Fluorescence Polarization Immunoassay
Assay Range	350 -2000ng/mL (complements low range assay, 25 – 500 ng/ml)	25 - 1500 ng/mL

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

- Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA dated September 16, 2002.
- Guidance for Industry and FDA Staff - Use of Symbols on Labels and in Labeling of In

- Vitro Diagnostic Devices Intended for Professional Use dated November 30, 2004
- Stability Testing of In Vitro Diagnostic Reagents (13640)
 - Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
 - Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)
 - Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)
 - Medical devices - Risk management - Part 1: Application of risk analysis (14971-1) EN 1441:1997, Medical Devices - Risk Analysis (EN 1441:1997)
 - Medical Devices - Symbols to be used with medical device labels, labeling and information to be supplied (15223)
 - Continuous Quality Improvement: Essential Management Approaches; Approved Guideline (GP 22-A)

L. Test Principle:

The automated Dimension® CSAE method uses an immunoassay technique in which free and CSA-bound antibody-enzyme species are separated using magnetic particles. The assay is performed using a method-specific Flex® reagent cartridge. The Flex® cartridge contains a pretreatment reagent, β-galactosidase-CSA antibody conjugate, CSA immobilized on chromium dioxide particles, chlorophenol red β-d-galactopyranoside(CPRG) substrate, and diluent to hydrate the tablets.

To perform the CSAE assay, a sample cup containing the whole blood sample to be analyzed and a CSAE Flex® reagent cartridge are placed on the Dimension® system. The Dimension® system mixes and lyses the whole blood sample. The lysed sample is then mixed with the antibody conjugate reagent to bind CSA present in the sample. Magnetic particles coated with CSA are added to bind free (unbound) antibody-enzyme conjugate. The reaction mixture is then separated magnetically. Following separation, the supernatant containing the CSA-antibody-enzyme complex is transferred to another cuvette and mixed with the substrate. β-galactosidase catalyzes the hydrolysis of CPRG (chlorophenol red β-d- galactopyranoside) to produce CPR (chlorophenol red) which absorbs light maximally at 577nm. The change in absorbance at 577nm due to the formation of CPR is directly proportional to the amount of CSA in the patient sample and is measured using a bichromatic (577,700nm) rate technique.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
 - a. *Precision/Reproducibility:*
Imprecision studies were based on CLSI Guideline EP5-A. CSA spiked whole pooled blood and commercial control materials were used in a total of two assays per day, two replicates per assay, over 20 days, calibrated twice. Imprecision results were within the acceptance criteria set by the sponsor. Results are summarized in the table below:

Imprecision of the Dimension CSAE Assay

Sample	Mean	Within-Run		Total	
		Std Dev	CV	Std Dev	CV
	ng/mL	ng/mL	%	ng/mL	%
Blood Pool 1	368.0	12.2	3.3	19.0	5.2
Blood Pool 2	1123.3	30.6	2.7	57.2	5.1
Blood Pool 3	1750.1	46.7	2.7	104.1	6.0
QC Level 1	488.7	14.0	2.9	28.8	5.9
QC Level 2	866.1	18.6	2.2	47.7	5.5
QC Level 3	1301.9	34.4	2.6	68.9	5.3

b. Linearity/assay reportable range:

Standard solutions were prepared by sequential mixing to create equally spaced sample pools starting with a high and low pool of known analyte concentration. Theoretical concentrations were computed for all intermediate pools based on the initial concentrations of the high and low pools.

The linearity of cyclosporine A on the Dimension® RxL by the Dimension® CSAE assay was evaluated by comparing observed versus expected values across the assay range. A linear regression analysis was performed on the data and plotted. The observed linearity across the reportable range has a correlation coefficient of 0.998, slope of 1.01, an intercept of -23.26, and a deviation from the estimated line of 0.054 ng/mL [0.045 nmol/L] with 95% confidence. The assay range claim is 350.0 ng/mL [291.7 nmol/L] to 2000 ng/mL [1664.0 nmol/L].

To test recovery, known amounts of CSA were added to human whole blood samples with concentrations of 610.0, 1232.2, and 1861.8 ng/mL [507.5, 1025.2, 1861.8 nmol/L]. Final CSA concentrations were measured. The calculated percent recovery ranged from 94.3% to 105.6% with a mean recovery of 101.0%.

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

The shelf life of the Dimension CSAE flex reagent cartridge is 12 months based on real time stability testing of three lots of product.

Calibrators for this assay were evaluated in k052015. The assay method is traceable to an internal protocol described in that submission.

d. Detection limit:

The functional sensitivity of the assay was demonstrated to be below the lower end of the assay range (<350 ng/mL). Patient samples greater than 2000 ng/mL CSA will generate an “Above Assay Range” test result. The manufacturer recommends manual 1:1 dilution of the sample with CSAE Calibrator Level 0 (diluent) and re-assaying the diluted sample. Laboratory experiments showed that the method had a consistent linear dilution profile

and acceptable recovery of diluted samples.

e. Analytical specificity:

Cross reactivity of CSAE with the six major metabolites of CSA (M1, M8, M17, M21, AM1c, and AM1c9) was established by spiking the metabolites into whole blood containing 500 ng/mL CSA. Cross-reactivity was between 2.1% and 4.7%, within the manufacture's specifications.

Dimension® CSAE was evaluated for interference according to CLSI EP7-A where bias is defined as the difference between the control sample (without the interferent) and the test sample that contains the interferent expressed as a percentage. Bias exceeding 10% was considered interference. Whole pooled blood spiked with 800 ng/mL CSA was used to demonstrate that the substances in the table below do not interfere with the CSAE assay at the concentrations listed:

Non-Interfering Substances: CSAE Assay	
Acetaminophen 20 mg/dL	Amikacin Sulfate 100 mg/mL
Amphotericin B 100 mg/mL	Ampicillin 5 mg/dL
Apresoline 100 mg/mL	Ascorbic Acid 3 mg/dL
Azathioprine 100 mg/mL	Bilirubin 60 mg/dL
Caffeine 10 mg/dL	Carbamazepine 12 mg/dL
Cephalosporin 100 mg/mL	Chloramphenicol 25 mg/dL
Chlordiazepoxide 2 mg/dL	Chlorpromazine 5 mg/dL
Cholesterol 475 mg/dL	Cimetidine 10 mg/dL
Creatinine 30 mg/dL	Dextran 75 2500 mg/dL
Diazepam 2 mg/dL	Digoxin 5 ng/mL
Digitoxin 100 mg/mL	Dipyridamole 100 mg/mL
Disopyramide 100 mg/mL	Erythromycin 20 mg/dL
Ethanol 350 mg/dL	Ethosuximide 30 mg/dL
FK506 (Tacrolimus) 0.1 mg/mL	Furosemide 2 mg/dL
Gentamicin 12 mg/dL	Heparin 8000 U/L
Ibuprofen 40 mg/dL	Immunoglobulin G 12 g/dL
Kanamycin A 100 mg/mL	Kanamycin sulfate B 100 mg/mL
Ketoconazole 100 mg/mL	Lidocaine 6 mg/dL
Lincomycin 100 mg/mL	Lipemia 1500 mg/dL (triglyceride)
Lithium 3.5 mg/dL	Methotrexate 100 mg/mL
Methylprednisolone 100 mg/mL	Mycophenolic Acid 100 mg/mL
N-acetyl procainamide 100 mg/mL	Neomycin sulfate 100 mg/mL
Nicotine 2 mg/dL	Oxytocin 100 mg/mL
Penicillin G 25 U/mL	Pentobarbital 10 mg/dL
Phenobarbital 15 mg/dL	Phenytoin 10 mg/dL
Prazosin 100 mg/mL	Prednisolone 100 mg/mL
Prednisone 100 mg/mL	Primidone 10 mg/dL
Procainamide 100 mg/mL	Propoxyphene 0.4 mg/dL

Non-Interfering Substances: CSAE Assay	
Propranolol 100 mg/mL	Protein (Albumin) 6 g/dL
Protein (Total) 4 g/dL	Protein (Total) 12 g/dL
Quinidine 100 mg/mL	Rapamycin 0.1 mg/mL
Rheumatoid Factor 500 IU/mL	Rifampin 100 mg/mL
Salicylic Acid 50 mg/dL	Spectinomycin 100 mg/mL
Streptomycin 100 mg/mL	Theophylline 25 mg/dL
Tobramycin 100 mg/mL	Tocainide 100 mg/mL
Triamterene 100 mg/mL	Urea 500 mg/dL
Uric Acid 20 mg/dL	Valproic Acid 50 mg/dL
Vancomycin 100 mg/mL	Verapamil 100 mg/mL

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

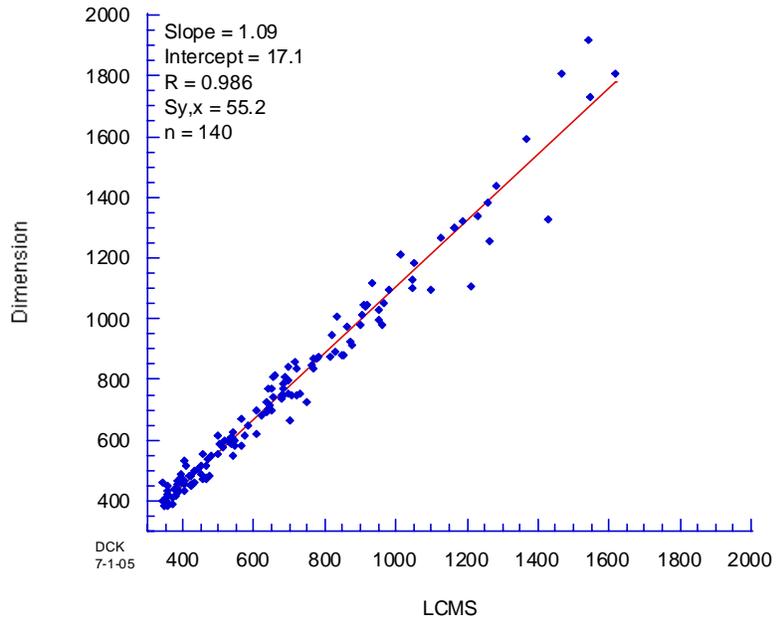
Two clinical studies were run at two large university hospitals. Patients (n=140 total) enrolled were heart, liver, or kidney transplant patients receiving cyclosporine therapy with CSA concentration ranges between 350ng/mL and 2000ng/mL. Studies were performed using routine methods for quality control, maintenance and calibration as described in the instrument instructions for use. Samples were tested with the Dimension® CSAE assay on a Dimension® clinical chemistry systems located at both external sites. All samples were also tested at one site with the predicate assay and at the other site by LC/MS technology.

Results presented in the graphs and table below include all organ types and both clinical sites. There was some variability between organ types. Regression analysis was comparable between the two clinical sites.

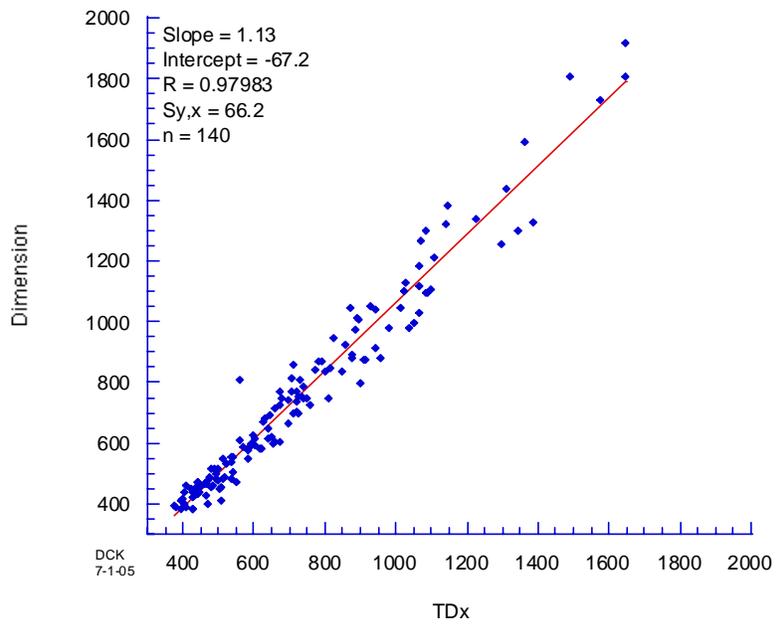
**Regression Statistics Summary By Organ Type:
Combined Clinical Sites versus Reference Method and Predicate**

Comparator	Slope	Intercept (ng/mL)	Correlation Coefficient	n
LCMS				
All	1.13	-67.2	0.980	140
Heart	0.996	2.52	0.982	35
Liver	1.11	-61.7	0.970	40
Kidney	1.09	-32.3	0.973	60
Predicate				
All	1.09	17.1	0.986	140
Heart	0.93	93.7	0.983	35
Liver	1.00	59.9	0.980	40
Kidney	1.10	15.2	0.990	60

**Dimension RxL vs LCMS Combined Data All Samples
Washington Univ. and Univ of Wisconsin CSAE**



**Dimension RxL vs TDx Combined Data All Samples
Washington Univ. and Univ. of Wisconsin CSAE**



- b. Matrix comparison:*
Not applicable. This reagent is only for use with whole blood in EDTA collected by normal procedures.
- 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 sponsor provides the following statement in the labeling regarding Expected Values:

There is no universally established therapeutic range for cyclosporine in whole blood. Values obtained with different assay methods cannot be used interchangeably due to differences in assay methods and reagent specificity. Individual cyclosporine 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 and each user must establish his or her own ranges based on these clinical experiences. Because of varying patterns of cross-reactivity with metabolites, the consistent use of one assay for individual patients is recommended. Conversion factors obtained from assay method comparisons should not be used to predict values for individual patients. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of cyclosporine, co-administration of other immunosuppressants, type of transplant, time post-transplant, and a number of other factors contribute to different requirements for optimal blood levels of cyclosporine.

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.