CEDIA® Cyclosporine PLUS Assay

Thermo SCIENTIFIC

IVD **For In Vitro Diagnostic Use**

Rx Only

REF 100147

Intended Use

The CEDIA® Cyclosporine PLUS assay is for the in vitro quantitative determination of cyclosporine in human whole blood using automated clinical chemistry analyzers as an aid in the management of cyclosporine therapy in kidney, liver, and heart transplants.

Summary and Explanation of The Test

Cyclosporine is a hydrophobic cyclic undecapeptide of fungal origin with immunosuppressive properties.[1-2] Although its mechanism of action is still under investigation, cyclosporine appears to affect the metabolism of T-helper lymphocytes and T-suppressor lymphocytes, resulting in an impairment of the immune system.[3-5] The immunosuppressive properties of cyclosporine make it a very effective drug for the treatment of certain autoimmune diseases and reducing the incidence of tissue rejection following organ transplantation. Cyclosporine therapy has optimal safety and efficacy over a narrow range of concentrations and may lead to a number of adverse effects.[6,7] The most critical adverse effects are organ rejection from inadequate dosing, or nephrotoxicity and hepatotoxicity, which become more probable as the drug concentration is increased.[8-11] Cyclosporine is administered either orally or intravenously. Since absorption and hepatic metabolism of the drug are highly variable from patient to patient, there is a poor correlation of blood levels with the administered dose.[12] Factors affecting cyclosporine concentrations in the blood include the nature of the transplant, the age and general health of the patient, and the co-administration of drugs such as carbamazepine, phenytoin, phenobarbital, erythromycin, rifampin, cimetidine and ketoconazole.[13-17] It is essential to monitor cyclosporine in organ transplantation to achieve optimal immunosuppressive effects in patients.[18-20]

The measurement of cyclosporine concentrations in whole blood in conjunction with other laboratory data and clinical evaluation is the best approach to optimize immunosuppression and minimize adverse side effects for recipients of organ transplants.

The CEDIA Cyclosporine PLUS assay uses recombinant DNA technology (US Patent No. 4708929) to produce a unique homogeneous enzyme immunoassay system.[21] The assay is based on the bacterial enzyme ß-galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociate to form fully active enzymes that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotometrically.

In the assay, analyte in the sample competes with analyte conjugated to one inactive fragment of ß-galactosidase for antibody binding site. If analyte is present in the sample, it binds to antibody, leaving the inactive enzyme fragments free to form active enzymes. If analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the reassociation of inactive ß-galactosidase fragments, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of analyte present in the sample.

Reagents

1. **EA Reconstitution Buffer:** Contains MOPS [3-(N-morpholino) propanesulfonic acid buffer], 0.50 µg/mL mouse monoclonal anti-cyclosporine antibodies, stabilizer, and preservative, 1 x 41 mL.
- **1a EA Reagent:** Contains 0.171 g/L Enzyme Acceptor (microbial), buffer salts, and preservative, 1 x 41 mL.
2. **ED Reconstitution Buffer:** Contains MES [2-(N-morpholino) ethanesulfonic acid buffer], detergent, and preservative, 1 x 19 mL.
- **2a ED Reagent:** Contains 52 µg/L Enzyme Donor(microbial) conjugated to cyclosporine, 2.73 g/L chlorophenol red-ß-D-galactopyranoside, stabilizers, and preservative, 1 x 19 mL.
3. **Lysing Reagent:** Contains buffer salts, detergents, and preservative, 1 x 98 mL.
4. **Low Range A Calibrator:** Contains 0.45 g BSA and 0.063 µg Cyclosporine A.
5. **Low Range B Calibrator:** Contains 0.45 g BSA and 1.125 µg Cyclosporine A.

Additional Materials:

Two (2) empty 20 mL analyzer bottles.

Additional Materials Required (but not provided):

REF	Kit Description
100012	CEDIA Cyclosporine PLUS High Range Calibrator Kit

Automated clinical chemistry analyzer

Commercial Control(s). Consult Thermo Fisher Scientific Technical Support for recommendations on suitable control material.

⚠ Precautions and Warnings

Exercise the normal precautions required for handling all laboratory reagents.

DANGER: EA Powder reagent contains ≤1.0% w/w sodium azide. ED Powder reagent contains 55% w/w bovine serum albumin (BSA). EARB Liquid reagent contains 0.75% bovine serum (fetal), <0.1% CsA Antibody (mouse monoclonal) and <0.13% sodium azide. EDRB and Lysing Liquid reagents contain <0.13% sodium azide. Calibrators contain 18% bovine serum albumin (BSA) and ≤0.13% sodium azide.

H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H412 - Harmful to aquatic life with long lasting effects.
EUH032 - Contact with acids liberates very toxic gas.

Avoid breathing dust/mist/vapor/spray. Contaminated work clothing should not be allowed out of the workplace. Avoid release to the environment. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Reagent Preparation and Storage

Refer to the specific instrument application sheet for assay parameters. Prepare the following solutions using cold reagents and buffers. Remove the kit from refrigerated storage (2-8°C) immediately prior to preparation of the working solutions.

In the case of accidental spill, clean and dispose of material according to your laboratory's SOP, local, and state regulations.

In the case of damaged packaging on arrival, contact your technical support representative (refer to back page of this PI).

Prepare the solutions in the following order to minimize possible contamination.

R2 Enzyme donor solution: Connect Bottle 2a (ED Reagent) to Bottle 2 (ED Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 2a is transferred into Bottle 2. **Avoid the formation of foam.** Detach Bottle 2a and adapter from Bottle 2 and discard. Cap Bottle 2 and let stand approximately 5 minutes at room temperature (15-25°C). Mix again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C) and let stand 15 minutes before use.

R1 Enzyme acceptor solution: Connect Bottle 1a (EA Reagent) to the 70 mL Bottle 1 (EA Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 1a is transferred into Bottle 1. **Avoid the formation of foam.** Detach Bottle 1a from adaptor. Discard Bottle 1a.

Cap filled Bottle 1 and let stand approximately 5 minutes at room temperature (15-25°C). Mix gently again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C). Allow reagent to stand on analyzer at least 15 minutes before use.

If your analyzer cannot accommodate the 70 mL bottle (bottle 1), two (2) empty smaller trapezoidal style bottles have been included. Decant the contents of the larger bottle 1 into each of the 2 smaller bottles dividing the volume equally between the two bottles.

Lysing Reagent: The lysing reagent is liquid and does not require reconstitution. Mix the contents of the bottle before each use by gently inverting the bottle 2-3 times. Record the date that the lysing reagent was opened on the bottle label. Remove the cap and dispense the required quantity of the lysing reagent into a sample cup as specified in the appropriate CEDIA Cyclosporine PLUS application sheet.

Barcode Usage: The barcodes on the reagents bottles are for the Low Range Assay. Reagent labels have a dedicated system barcode that most analyzers will ignore if unrecognized. If the analyzer returns an error code, overlay the barcode with solid-colored tape. Contact Technical Services for assistance if needed.

NOTE 1: The components supplied in this kit are intended for use as an integral unit. **Do not mix components from different lots.**

NOTE 2: Avoid cross-contamination of reagents by matching reagent caps to the proper reagent bottle. The R2 solution (Enzyme Donor) should be yellow-orange in color. A red or purple-red color indicates that the reagent has been contaminated and must be discarded.

NOTE 3: The R1 and R2 solutions must be at the reagent compartment storage temperature of the analyzer before performing the assay. Refer to the analyzer specific application sheet for additional information.

NOTE 4: Prepare R2 solution prior to R1 solution.

NOTE 5: To ensure reconstituted EA reagent stability, protect from prolonged continuous exposure to bright light.

Store reagents at 2-8°C. **DO NOT FREEZE.** For stability of the unopened components, refer to the box or bottle labels for the expiration date.

R1 Solution: 60 days refrigerated at 2-8°C.
R2 Solution: 60 days refrigerated at 2-8°C.
Lysing Reagent: 60 days at 2-30°C.
Calibrators: 60 days at 2-8°C.

Specimen Collection and Handling
Use whole blood treated with EDTA.[22] Care should be taken to preserve the integrity of the specimen from the time it is collected until the time it is assayed. Specimens should be labeled with both the time of blood collection and time of last drug administration. Specimens should be capped, assayed within 7 days when stored at 2-8°C, or within 1 month when stored at -20°C. Avoid repeated freezing and thawing. Do not induce foaming of samples.

Sample Preparation
1. Allow calibrators, controls and patient samples to come to room temperature.
2. Mix the sample (calibrators, controls, or patient sample) gently butthoroughly before use.
3. Pipette exactly 100 µL of the sample into a sample cup.
4. Using a repeater pipette, add exactly 400 µL of the CEDIA Cyclosporine PLUS Lysing Reagent to each sample cup.
5. Vortex each cup thoroughly for 2-5 seconds.
6. Place the sample cups on the instrument and assay.

The hemolysate is stable for 1.5 hours at 15-25°C in the sample cup.[23]

The CEDIA Cyclosporine PLUS assay is intended for use on automated clinical chemistry analyzers. Specific application performance data are on file at Microgenics Corporation, a part of Thermo Fisher Scientific.[23]

Assay Procedure
Contact Thermo Fisher Scientific Technical Support for application parameters.

Calibration
The CEDIA Cyclosporine PLUS assay produces a linear standard curve using the appropriate CEDIA Cyclosporine PLUS Kit Calibrators. Data reduction calculated from least squares linear regression can be achieved using analyzer software. Validate the assay calibration by testing commercial control(s) with established recovery ranges for the CEDIA Cyclosporine PLUS assay.

NOTE: Calibrator value assignment cards are included in each calibrator kit. Before using a new kit of calibrators, check your chemistry parameters to ensure the calibrator concentrations match the values on the value assignment card.

Calibration Frequency
Recalibration is recommended
- After reagent bottle change.
- After calibrator or reagent lot change.
- After monthly instrument maintenance is performed.
- As required following quality control procedures.

Reportable Range
The Low Assay reportable range is 25 ng/mL to 450 ng/mL. The minimum detectable concentration of the CEDIA Cyclosporine PLUS assay is 25 ng/mL.

The High Assay reportable range is 450 ng/mL to 2000 ng/mL.

Out of Range Samples
Specimens quantitating greater than the Cyclosporine PLUS High Calibrator can be reported as > 2000 ng/mL or diluted one part original sample with one part cyclosporine free whole blood, lysed and reassayed. If only Cyclosporine Low Range Assay is performed in the lab, out of range samples can be diluted one part original sample with 3 parts cyclosporine free whole blood, lysed and reassayed.

1. Mix the sample gently but thoroughly before use.
2. Prepare dilution by mixing one part volume of patient sample and one part volume of cyclosporine free whole blood OR one part volume of patient sample and 3 parts volume of cyclosporine free whole blood.
3. Using a repeater pipette, add exactly 400 µL of the CEDIA Cyclosporine PLUS Lysing Reagent to each sample cup.
4. Vortex each cup thoroughly for 2-5 seconds.
5. Place the sample cup(s) on the instrument and reassay.

The value obtained on reassay should be derived as follows:

$$\text{Actual Value} = \text{Dilution Factor} \times \text{Diluted Value}$$

$$\text{Dilution Factor} = \frac{\text{(Volume of Sample + Volume of cyclosporine free whole blood)}}{\text{Volume of Sample}}$$

Specimens giving values below the minimum detectable concentration of the assay should be reported as < 25 ng/mL.

Quality Control and Calibration
Each laboratory should establish its own control frequency.

Good laboratory practice suggests that at least two levels (low and high medical decision points) of quality control be tested each day patient samples are assayed and each time a calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover with the specified range, review all operating parameters. Contact Thermo Fisher Scientific Technical Support for further assistance and recommendations on suitable control material. All quality control requirements should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

NOTE: Reassess control targets and ranges following a change of reagent lot.

Results and Expected Values
Refer to the appropriate operator's manual or analyzer-specific protocol for detailed calculation information.

Limitations [23]
The CEDIA Cyclosporine PLUS assay performance has not been established with body fluids other than human EDTA whole blood.
Criterion: Recovery ±15 ng/mL of initial value at concentrations < 150 ng/mL or ± 10% of initial value concentrations > 150 ng/mL.
Icterus: No significant interference up to I index of 60 (approximate unconjugated bilirubin concentration: 60 mg/dL).
Lipemia: No significant interference from triglycerides up to 1000 mg/dL. No significant interference from cholesterol up to 300 mg/dL. High levels of triglycerides and cholesterol may result in low quantitation.
Total Protein: < 10 g/dL does not interfere. High levels of protein may result in low quantitation. Rheumatoid factor: < 100 IU/mL do not interfere.
Hematocrit range: 30.5% to 53.5%. Higher hematocrit levels may result in low quantitation. For patients who may have metabolite accumulation, for example those with impaired liver function, unexpectedly high drug values, or increased time post therapy, use of this assay may be supported with a method that is highly specific for the parent compound, such as HPLC.

The incidence of patients having antibodies to E. coli ß-galactosidase is extremely low. However, some samples containing such antibodies can result in artificially high results that do not fit the clinical profile. If this occurs, contact Thermo Fisher Scientific Customer Technical Support for assistance.

As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which could cause falsely elevated results. Care should be taken to insure the blood draws are taken at consistent intervals after administration of cyclosporine.

Expected Values
No firm therapeutic range exists for cyclosporine in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of cyclosporine, coadministration of other immunosuppressants, type of transplant, time post transplant, and a number of other factors will cause different requirements for optimal blood levels of cyclosporine. 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 ranges based on clinical experience.[24] Ranges will vary according to the commercial test used. Conversion factors should not be used to predict values for individual patients. Consistent use of one assay for an individual patient is recommended because of varying patterns of cross-reactivity with metabolites.

Specific Performance Characteristics [23]
Typical performance data obtained on the Hitachi 911 analyzer are shown below. The results obtained in your laboratory may differ from these data. For additional analyzer specific performance data, refer to the analyzer specific application protocol.

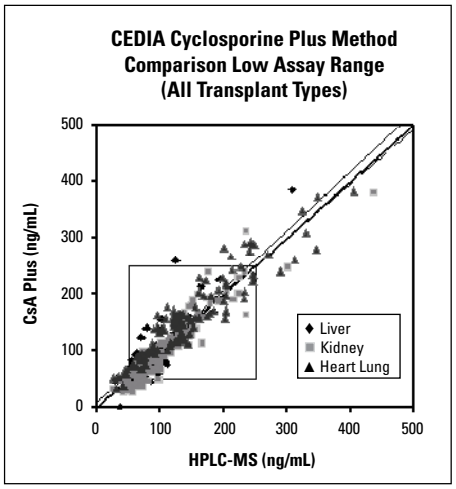
Precision
Measured precision studies using packaged reagents, pooled whole blood and whole blood controls yielded the following results in ng/mL: Hitachi 911 analyzer (37°C) NCCLS modified replication experiment, EP5-T (3 replicates, daily for 21 days).

Low Range Assay			Within Run		Total	
Sample	n	$\bar{x}$	SD	CV%	SD	CV%
CI	63	46.2	3.7	8.0	7.4	16.0
CII	63	199.7	5.9	2.9	9.1	4.6
Low Pool	63	54	4.7	8.8	6.6	12.2
High Pool	63	434.7	6.7	1.6	19.4	4.5

High Range Assay			Within Run		Total	
Sample	n	$\bar{x}$	SD	CV%	SD	CV%
CIII	63	418	31.7	7.6	40.5	9.6
CIV	63	642	38.0	5.9	47.0	7.3
CV	63	1257	49.9	4.0	63.9	5.1
Low Pool	63	472	22.8	4.8	35.1	7.5
High Pool	63	1695	39.2	2.3	87.3	5.2

Method Comparison-Low Assay Range

Comparisons using Microgenics CEDIA Cyclosporine PLUS (y) to HPLC-MS (x) at four sites provided the following correlation.



CEDIA Cyclosporine Plus Low Range Assay

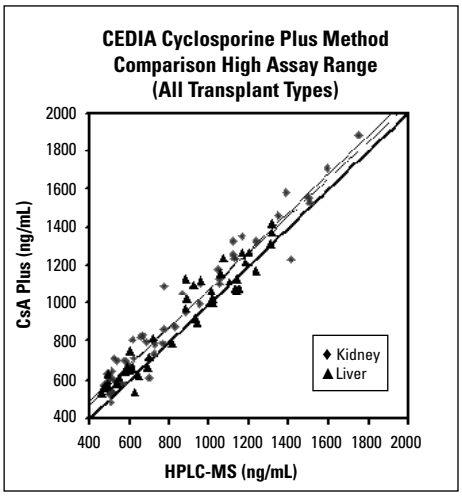
Comparisons using Microgenics CEDIA Cyclosporine PLUS (y) to FPIA (x), EMIT® (x), and HPLC-MS (x) at four sites provided the following correlations.

Transplant Type	x-Axis	Linear Regression $S_{y.x}$	Deming's $S_{y.x}$	r	n	Range
All	HPLC-MS	0.97x + 8 27	1.05x - 2 27	0.93	311	25-386 ng/mL
All	EMIT	1.05x + 6 16	1.09x + 2 11	0.97	298	33-412 ng/mL
All	Axsym	1.00x + 2 19	1.05x - 5 13	0.95	296	35-368 ng/mL
All	TDx	0.87x - 18 20	0.91x - 25 15	0.95	298	9-386 ng/mL
Heart/Lung	HPLC-MS	0.87x + 32 26	0.93x + 24 26	0.94	109	31-383 ng/mL
Liver	HPLC-MS	1.10x + 0.9 25	1.30x - 18 26	0.88	80	41-386 ng/mL
Kidney	HPLC-MS	1.02x - 9 24	1.09x - 17 16	0.94	122	25-379 ng/mL

The Low Range assay method comparison to HPLC-MS population includes: 311 samples with ages between 18 and 77. Represented are 107 acute, 195 chronic, 109 heart-lung, 80 liver, and 122 kidney transplant samples drawn from 228 individuals at trough levels.

Method Comparison-High Assay Range

Comparisons using Microgenics CEDIA Cyclosporine PLUS (y) to HPLC-MS (x) provided the following correlation.



CEDIA Cyclosporine Plus High Range Assay

Comparisons using Microgenics CEDIA Cyclosporine PLUS (y) to FPIA (x), EMIT® (x), and HPLC-MS (x) at four sites provided the following correlations.

Transplant Type	x-Axis	Linear Regression $S_{y.x}$	Deming's $S_{y.x}$	r	n	Range
All	HPLC-MS	0.97x + 98 81	1.01x + 71 57	0.97	93	486-1882 ng/mL
All	EMIT	1.00x + 12 28	1.00x + 11 20	0.99	343	12-1979 ng/mL
All	Axsym	1.04x - 2 30	1.05x - 4 21	0.99	344	3-1857 ng/mL
All	TDx	0.96x - 33 36	0.97x - 35 26	0.99	334	15-1932 ng/mL
Liver	HPLC-MS	0.94x + 99 73	0.98x + 70 52	0.96	46	529-1417 ng/mL
Kidney	HPLC-MS	0.99x + 107 82	1.02x + 84 58	0.97	47	486-1882 ng/mL

The High Range assay method comparison to HPLC-MS population includes: 93 samples with ages between 30 and 72. Represented are 83 acute, 8 chronic, 46 liver and 47 kidney transplant samples drawn from 21 individuals within 8 hours of administration of cyclosporine.

Linearity

To assess the linearity, a high cyclosporine patient pool was diluted with a drug-free whole blood sample for the Low Range assay; for the High Range assay a cyclosporine patient pool was used for dilution. The percent recovery was then determined by dividing the assayed value by the expected value. The expected values were generated off the slope and intercept of the regression of the assayed values.

	Low Assay Range			High Assay Range		
% High Sample	Expected Value (ng/mL)	Assayed Value (ng/mL)	% Recovery	Expected Value (ng/mL)	Assayed Value (ng/mL)	% Recovery
100.0	433	433	100.0	1930	1930	100.0
90.0	390	386	99.1	1782	1785	100.2
80.0	347	332	95.5	1633	1708	104.6
70.0	304	298	97.9	1485	1573	105.9
60.0	261	263	100.6	1337	1361	101.8
50.0	218	222	101.6	1189	1244	104.7
40.0	176	184	104.6	1040	1028	98.8
30.0	133	129	97	892	906	101.6
20.0	90	89	99.1	744	775	104.2
10.0	47	47	99.7	595	599	100.6
0.0	4	4	100.0	447	447	100.0

Recovery

To assess the recovery of the assay, cyclosporine was added to 21 normal whole blood samples. For each set of 21 samples, cyclosporine was spiked in as indicated in the table. The percent recovery was determined by dividing the mean dose of each set of 21 spike samples by the theoretical amount of cyclosporine spiked in the samples.

Low Assay Range			High Assay Range		
N	21	21	N	21	21
Target, ng/mL	150	300	Target, ng/mL	600	1600
x (ng/mL)	141	308	x (ng/mL)	590	1570
% Recovery	94	103	% Recovery	98	98

Specificity

The following compounds have been tested for cross-reactivity in the CEDIA Cyclosporine PLUS assay through in vitro spiking into whole blood samples containing approximately 200 ng/mL cyclosporine.

Compound	Tested Concentration (ng/mL)	% Cross-Reactivity
AM 1	1000	4.4
AM 9	1000	20
AM 4n	1000	16
AM 19	1000	0.9
AM 4N9	1000	1.0
AM 1c	1000	1.6

Compound	Tested Concentration (ng/mL)	Observed Dose (ng/mL)	% Cross-Reactivity
Acetominophen	100000	-0.2	< 0.015
Amikacin Sulfate	100000	0.7	< 0.015
Ampicillin	100000	0.4	< 0.015
Azathioprine	100000	-5.2	< 0.015
Carbamazepine	100000	-2.8	< 0.015
Chloramphenicol	100000	-1.3	< 0.015
Cimetidine	100000	1.7	< 0.015
Digitoxin	100000	-1.2	< 0.015
Digoxin	100000	-1.4	< 0.015
Dipyridamide	100000	-4.1	< 0.015
Disopyramide	100000	-3.3	< 0.015
Erythomycin	100000	-2.8	< 0.015
FK506	20000	3.8	< 0.075
Furosemide	100000	-4.2	< 0.015
Gentamicin	100000	-1.1	< 0.015
Kanamycin	100000	0.1	< 0.015
Kanamycin Sulfate B	100000	0.7	< 0.015
Ketoconazole	100000	-0.9	< 0.015
Lidocaine	100000	-1.6	< 0.015
Methylprednisolone	100000	-0.6	< 0.015
Morphine Sulfate	100000	-5	< 0.015
Mycophenolic Acid	50000	-4.7	< 0.030
N-acetylprocainamide	100000	-1.3	< 0.015
Penicillin-G (Sodium Salt)	100000	-0.8	< 0.015
Phenobarbital	100000	-10.1	< 0.015
Phenytoin	100000	-3.1	< 0.015
Prazosin	100000	-0.7	< 0.015
Prednisolone	100000	-2.4	< 0.015
Prednisone	100000	-0.8	< 0.015
Procainmide HCL	100000	-2.8	< 0.015
Quinidine Sulfate	100000	-1.6	< 0.015
Rapamycin	5000	-4.8	< 0.300
Rifampicin	60000	-7.3	< 0.025
Salicylic Acid	100000	-0.7	< 0.015
Spectinomycin	100000	-0.5	< 0.015
Streptomycin Sulfate	100000	1.1	< 0.015
Theophylline	100000	0.2	< 0.015
Tobramycin	100000	0.2	< 0.015
Triamterene	100000	-1.6	< 0.015
Valproic Acid	100000	-1.3	< 0.015
Vancomycin HCL	100000	0	< 0.015
Verapamil	100000	-0.3	< 0.015

Sensitivity

The minimum detectable concentration of the CEDIA Cyclosporine PLUS Assay is 25 ng/mL. The value was determined by calculating the concentration of cyclosporine which would give a response equal to two standard deviations of the low calibrator. The functional sensitivity which is the lowest concentration with an inter-assay CV of 20% is 40 ng/mL.

Reference

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Glossary:

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